Respiration in Spinal Cord Injury:

time-courses and training

Gabi Mueller

Respiration in Spinal Cord Injury:

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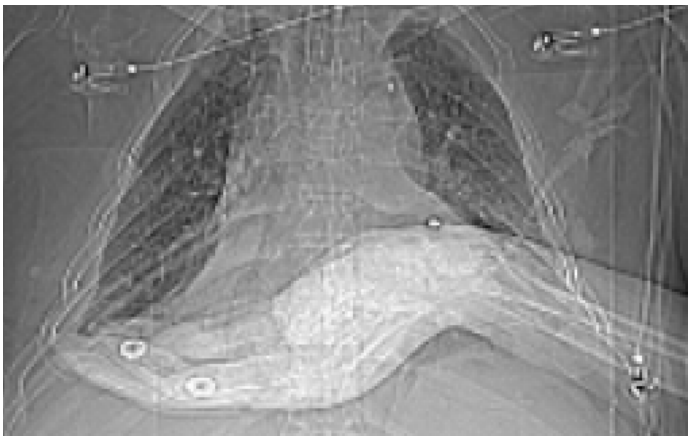


Chapter 1

General Introduction and

outline of the thesis

1.1 Spinal Cord Injury

Injuries to the spinal column often cause a disruption or compression of the medulla which results in loss of sensory, motor and autonomic function below the level of injury. Injuries to the cervical spinal cord can cause deficits in all four extremities (tetraplegia), while injuries to the thoracic or lumbar spinal cord affect the legs and, depending on the lesion level, also the muscles of the trunk (paraplegia). Persons with tetraplegia are injured between the first and the eighth cervical spinal vertebra (C1-C8) and individuals with paraplegia between the first thoracic spinal vertebra and the fifth lumbar spinal vertebra (T1-L5) (Figure 1). Neurological level and completeness of an injury largely determine functional independence after a spinal cord injury (SCI). The classification of a SCI is based on the lowest intact spinal segment for motor and sensory function respectively. In order to better classify impairments related to the different lesion levels, including information about completeness of motor and sensory functioning, the American Spinal Injury Association (ASIA) defined a so called 'ASIA impairment scale' (12) that consists of 5 categories (Table 1).

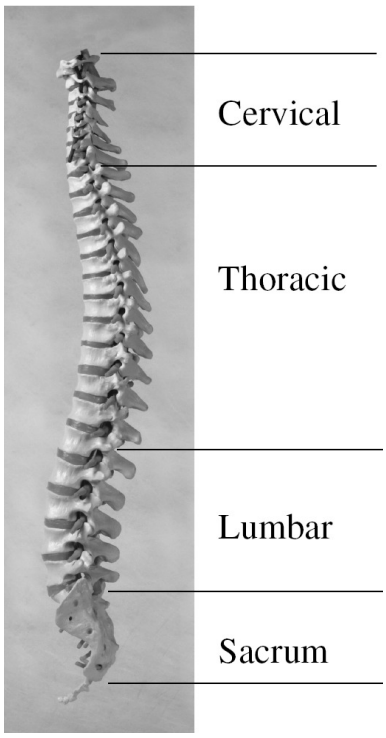


Figure 1: The spinal cord with indication of segments

Table 1: ASIA impairment scale

	Descriptions of categories
ASIA A	Complete injury where no sensory or motor function is preserved in sacral segments S4-S5.
ASIA B	Incomplete injury where sensory, but not motor function is preserved below the neurologic level and extends through sacral segments S4-S5.
ASIA C	Incomplete injury where motor function is preserved below the neurologic level and most key muscle below the neurologic level have muscle grade less than 3 (active full range movements against gravity).
ASIA D	Incomplete injury where motor function is preserved below the neurologic level and most key muscles below the neurologic level have muscle grade greater than or equal to 3.
ASIA E	Normal sensory and motor functions.

Both in the U.S. and the Netherlands incomplete tetraplegia represents the most frequent category of patients, followed by complete paraplegia, complete tetraplegia and incomplete paraplegia (4, 136). As a result of the loss in sensory, motor and autonomic function below the lesion level, persons with a SCI experience lesion level dependent changes in bladder and bowel function, sexual function, gastrointestinal function, blood pressure, thermoregulation and breathing ability (142). Secondary complications such as deep vein thrombosis and autonomic dysreflexia, hypotension, osteoporosis, heterotopic ossification, contractures, pressure ulcers, pain, spasticity, atelectasis and pneumonia are further problems that often occur during the course of a SCI (33, 34, 63, 117, 135, 142, 161).

Epidemiology of SCI

The incidence of SCI is estimated to be approximately 40 cases per million population per year in the U.S. (4) and 30 cases per million persons per year in Switzerland (60). Interestingly, in the Netherlands and Ireland the incidence of SCI seems to be much lower with only 12 and 13 cases per million persons per year (152, 119). More consistent epidemiologic data regarding the difference between countries include the variables gender and age at injury. Generally, it is men (70-80%) rather than women (20-30%) that get affected by SCI (4, 28, 35, 136, 152). The mean age at injury for traumatic lesions lies between 20 and 30 years in the majority of cases (4, 35, 136). Non-traumatic lesions normally occur much later with a peak in the age group of 60 to 70 years (136). Injuries to the spinal cord may either be traumatic (motor vehicle accidents, falls, various sports accidents or gun shots) or non-traumatic (tumors, spinal stenosis, vascular or birth defects). Epidemiologic data of traumatic and non-traumatic SCI cases reported in literature varies widely (28, 35, 77, 136, 152). Schönherr et al. (136) reported a figure of 52% for non-traumatic causes for SCI in the Netherlands, while we know that in Switzerland the percentage of non-traumatic cases continuously rose over the last few years (50). A main difference in the rehabilitation of traumatic and non-traumatic SCI involves in the length of stay in the rehabilitation unit. Usually the rehabilitation of persons with non-traumatic SCI lasts much shorter than the rehabilitation of individuals with traumatic SCI (133, 136). Data from the Netherlands and Israel report an average of 85 and 106 days of inpatient rehabilitation for non-traumatic SCI, while their traumatic counterparts had a mean duration of 205 and 239 days of inpatient rehabilitation, respectively (133, 136). Length of stay for persons with traumatic SCI shows major differences between Europe and the U.S. (35). In contrast to the fairly long duration of inpatient rehabilitation in most European countries (200-400 days on average) (35, 133, 136), length of stay in the rehabilitation unit in the U.S. decreased from a mean of 115 days in 1974 to 39 days in 2004 (3). This big difference between European and U.S. countries in length of stay during inpatient rehabilitation may arise from differences in rehabilitation goals. Rehabilitation of SCI in European countries not only contains the restoration of physical

functioning, but also factors such as emotional adaptation to the new situation, regaining social independence and reintegration into the community which often includes adaptations in housing and the working place. Reintegration into the community and resumption of work are not only important contributing factors to the quality of life of each individual living with SCI on the one hand, but it also helps reducing health care costs that encumber the whole community. Another factor that continuously entails an increase in health care costs are rehospitalizations (113). The main causes of rehospitalisations after discharge from inpatient rehabilitation of individuals with SCI are diseases of the genitourinary and the respiratory system (25). Individuals with tetraplegia tend to be more frequently rehospitalized due to respiratory complications, while individuals with paraplegia commonly encounter diseases of the genitourinary system (25). Even though life expectancy in SCI increased drastically during the last decades due to various advances in medical and critical care, it still remains somewhat below the average of the able bodied population (48). Life expectancy decreases the lower the age at injury and the higher the lesion level (3). Ventilator dependency further reduces life expectancy regardless of lesion level (3). Mortality rates are significantly higher during the first year after injury than during the subsequent years (3.) The primary causes of death in the SCI population are pneumonia, pulmonary emboli and septicaemia (3, 47). Therefore, cardio-pulmonary tasks seem to be an important issue during and after SCI rehabilitation.

1.2 Respiratory mechanics and physiology in able bodied persons

Respiration is an essentially vital process and therefore respiratory muscles have to work continuously throughout the whole day. The coordinated action of respiratory muscle activity rhythmically moves the rib cage and the diaphragm to pump air in and out of the lungs. The chest wall mainly consists of the rib cage and the abdomen separated by the diaphragm and can be considered as one interacting system (37). During inspiration, the diaphragm moves caudally and the chest wall and anterior abdominal wall move outward. The diaphragm is the main respiratory muscle, that has to work continuously and consists of a dome and the zone of apposition (Figure 2) (37). During inspiration, the zone of apposition applies an expanding pressure on the lower rib cage which supports the action of the external intercostal muscles (37). The expansion of the rib cage essentially happens through an outward-upward

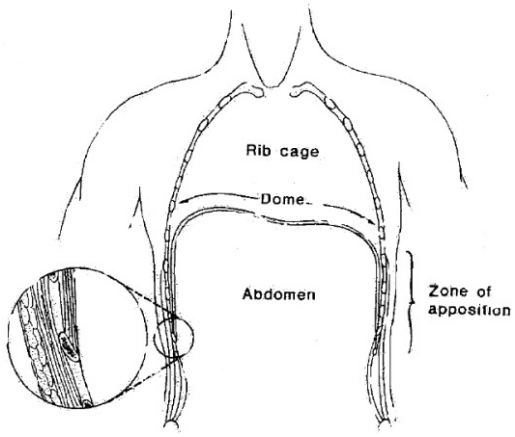


Figure 2: Dome and zone of apposition of the diaphragm. Reprinted with permission from Elsevier (37).

rotation of the ribs around the axis of the articulations with the vertebral bodies (87, 159) and thereby, together with the action of the diaphragm, increases the intra-thoracic volume (40). This increase of volume lowers the air pressure in the alveoli to below atmospheric pressure. Because air always flows from a region of high pressure to a region of lower pressure, it now rushes in through the respiratory tract and into the alveoli. In the alveoli gas exchange, i.e. oxygen uptake and carbon dioxide release, takes place. The process of inspiration is further supported by the sternocleidomastoids that elevate the sternum, the scalenes that elevate the top two ribs and the external intercostals and the pectorals that elevate further ribs and thereby open the chest wall. During expiration the thoracic cavity returns to its original volume, increasing the air pressure in the lungs, and forcing the air out. During resting breathing, expiration is mainly a passive process where the diaphragm moves cranially and returns to its initial relaxed position while the rib cage and the anterior abdominal wall move inward. Active expiration, e.g. during coughing or physical activity is further supported by the abdominal muscles that push the diaphragm up faster, the rectus abdominis that pulls down on the lower ribs and the internal intercostals that draw the ribs down.

1.3 Respiratory muscle training and fatigue

Respiratory muscles are, functionally and morphologically, skeletal muscles. Thus, respiratory muscles may fatigue in a similar way as skeletal muscles do, but they also improve their performance due to adequate training stimuli (2, 86, 104). Therefore, respiratory muscle training may follow the basic training principles acquainted with skeletal muscle training. The most important principle is that muscles only adapt when an adequate training stimuli that lies above a certain individual threshold is achieved. An adequate training stimulus may include an increase of duration, intensity or frequency of training. In accordance to skeletal muscles, respiratory muscles can be targeted for strength or endurance by specific training programs (93). Nevertheless, the rationale for isolated respiratory muscle training was not generally accepted in the last decades. Dempsey and Babcock postulated that the resources of the respiratory system are that high that they may not limit exercise performance (45), which was supported by many other publications (44, 49, 62, 72, 121, 123). Anyway, during the last two decades growing evidence showed that respiratory muscles fatigue during intensive physical exercise tasks (32, 98, 99, 110, 124), that respiratory muscle fatigue limits exercise performance (103, 108) and that respiratory muscle training increases exercise performance in healthy individuals (18-20, 64, 106, 112, 131, 144). Additionally it has been shown that physical exercise training induced changes in respiratory muscles and thus even intensive physical exercise training may be an adequate training stimulus for improvements in respiratory muscle performance (30, 88, 126). Of course respiratory muscle performance may also decrease over time due to deconditioning, e.g. when respiratory muscle training is stopped (2, 27, 66, 130) .

Respiratory muscle strength training in healthy humans

The principles of respiratory muscle strength training follow those of skeletal muscle strength training. Therefore, an adequate in- or expiratory pressure has to be obtained in order to achieve a training effect (15). Respiratory muscle strength training can be performed as inspiratory, expiratory or combined in- and expiratory muscle training. Nevertheless, in most respiratory muscle strength training studies subjects had to perform inspiratory muscle strength training (36, 43, 68, 90, 91). Respiratory muscle strength training can be performed with resistive loading or with threshold loading (122). During threshold loaded respiratory training, inspiratory pressure is independent of the flow rate and therefore the amount of resistance can not be altered by changing the breathing pattern, like it would be possible during resistive loaded breathing. The threshold loading method is presently the most commonly used method (122). Training stimuli showed to be task specific (130). Inspiratory muscle strength training significantly improved maximal inspiratory muscle pressure (Pi_{max}) (51, 64, 71, 93, 131, 156) and expiratory muscle strength training improved maximal expiratory muscle pressure (Pe_{max}) (93, 156). There is some evidence that resistive inspiratory muscle training may enhance cycling endurance exercise capacity (64, 131, 132). However, Williams et al. did not find any improvements in maximal running performance after resistive inspiratory muscle training in competitive athletes (158).

Respiratory muscle endurance training in healthy humans

Respiratory muscle endurance training is generally performed using normocapnic hyperpnoea (for details see 1.8 of this Introduction) (137). Performing normocapnic hyperpnoea training requires to maintain a ventilation level of 55-85% MVV for about 30 minutes (111, 137). This training has to be conducted 3 to 5 times a week for several consecutive weeks in order to increase the time of maximal sustainable normocapnic ventilation, which represents respiratory muscle endurance performance (126). Several studies showed that respiratory muscles fatigue during intensive endurance exercise tasks (31, 82, 86, 104, 124). Further, it is known that fatigued respiratory muscles may limit endurance exercise performance (103, 108). Therefore, specific respiratory muscle endurance training aiming to increase physical endurance exercise performance was assessed in several studies and showed improvements in respiratory muscle endurance performance (14, 19, 20, 59, 83, 88, 92, 93, 105, 115, 145, 149). Even though if all these studies reported significant increases in respiratory muscle endurance performance, not all found improvements in physical exercise endurance capacity after respiratory muscle endurance training (14, 59, 115, 143). Studies which investigated effects of normocapnic hyperpnoea training through physical exercise endurance tests at a very high intensity (i.e. 90-95% of peak oxygen uptake (VO_{2peak})), did not find any improvements in exercise performance (59, 72, 115). Accordingly, VO_{2peak} did not increase in most

normocapnic hyperpnoea training studies (19, 20, 59, 92, 106, 115, 145). In contrast to this, most studies that assessed effects of normocapnic hyperpnoea training in endurance exercise tests at intensities between 60 and 85% VO_{2peak} showed significant increases in endurance exercise performance after 4 to 8 weeks of normocapnic hyperpnoea training (19, 20, 83, 106, 112, 143, 145, 149). Controversies concerning the impact of normocapnic hyperpnoea training on exercise performance may also be caused by several other confounding factors such as training status of the subjects tested, duration and the amount of muscle mass used during the exercise performance test, the concept of the exercise performance test, i.e. whether an endurance test at a given intensity or a time-trial to exhaustion was performed, duration and intensity of the normocapnic hyperpnoea training and the duration between the last normocapnic hyperpnoea training and the exercise performance test. Of course low sample sizes may additionally diminish explanatory power of such studies. Unfortunately, all the studies mentioned above differed substantially in the factors that may influence the outcome of studies that are investigating the effects of normocapnic hyperpnoea training. Several studies measured various physiologic parameters in addition to respiratory and physical exercise endurance in order to understand the mechanisms by which physical exercise endurance is influenced by normocapnic hyperpnoea training (59, 106, 115, 143, 145, 149). These studies did not find any systematic effects from normocapnic hyperpnoea training on exercise performance which may be explained by changes in the heart (106) or the lung (149). Concerning changes in blood lactate concentrations after normocapnic hyperpnoea training, the literature reveals controversial findings (143, 145). Sonetti et al. (143) found no changes in blood lactate concentrations during an incremental or a constant work rate test after five weeks of combined respiratory muscle strength and endurance training. In contrast to this, Spengler et al. (145) reported significant decreases in blood lactate concentrations at the end of both an incremental as well as a constant work rate endurance test after four weeks of respiratory muscle endurance training. They speculated that these decreases in blood lactate concentrations may be caused by an improved lactate uptake by the trained respiratory muscles (145). Respiratory muscles mainly cosist of type I muscle fibres (2) which can use lactate as energy source. Thus, respiratory muscles may probably be used to fasten lactate removal and thus accelerate recovery after high intensity exercise bouts. Nevertheless, this assumption first has to be tested.

Another interesting approach is the one of Harms et al. about the competing situation between limb and respiratory muscles for their share of cardiac output (74-76). It is most likely that effects of normocapnic hyperpnoea training reduce oxygen costs of breathing, meaning that at the same exercise intensity respiratory muscles need less oxygen, i.e. a lesser percentage of cardiac output. Thus, limb muscles may work on a more aerobic level at a higher exercise intensity or sustain a given exercise intensity for a longer time. Changes in reflex sympathetic activation that reduce blood flow due to diaphragmatic fatigue are discussed as well as a factor decreasing exercise performance. This reduction may be caused by a reflex from the

diaphragm on the vegetative nervous system causing an increased sympathetic activity which may lead to a vasoconstriction in the leg muscles (138, 147). Changes in dyspnea and breathlessness or the perception of respiratory muscle effort due to normocapnic hyperpnoea training are discussed as a further possible factor that may influence exercise performance (19, 155). Nevertheless, physiologic mechanisms through which exercise performance may be enhanced after isolated normocapnic hyperpnoea training are not yet known in detail. Therefore, at the present time it is not yet possible to arrive at a conclusion regarding the effects of normocapnic hyperpnoea training on physical exercise performance in healthy individuals.

1.4 SCI and respiratory function

SCI can result in diminished pulmonary function due to lesion dependent paralysis of respiratory muscles. Persons with paraplegia miss function of the abdominal muscles and, depending on the lesion level, also of the intercostal muscles. Persons with tetraplegia lack most of the expiratory and even some of the auxiliary inspiratory muscles. The diaphragm is the main inspiratory muscle and innervated through the N. phrenicus between C3 and C5. Therefore, complete lesions above C4 require mechanical ventilation in most cases. The main respiratory muscles and their level of innervations are presented in Figure 3.

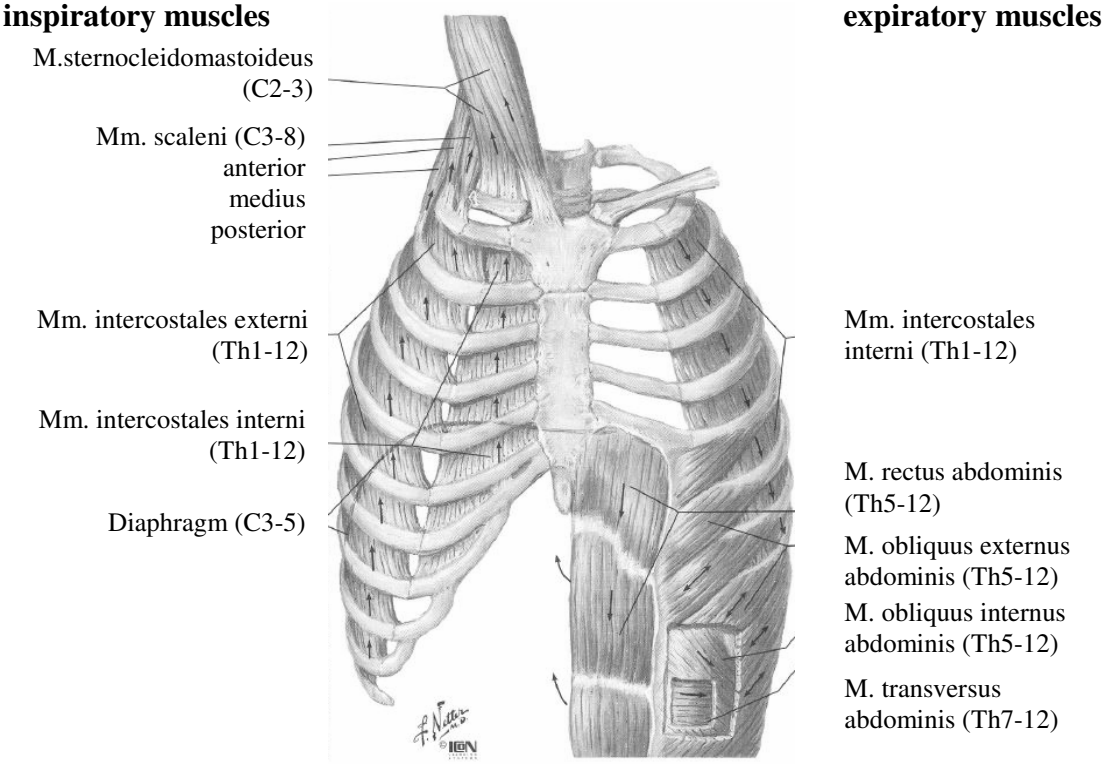


Figure 3: The main respiratory muscles and their innervation; Netter illustration used with permission of Elsevier Inc. All rights reserved.

Respiration seems to be one of the main problems in chronic SCI and especially in tetraplegia (78). Respiratory complications such as pneumonia, atelectasis and respiratory failure are major causes of morbidity and mortality in subjects with SCI (6, 61, 128). Such complications often arise because of an ineffective cough and secretion retention due to paralyzed expiratory muscles. They therefore become more severe with higher lesion level and early after injury (8, 94). Immediately after the event of a SCI 62% of all patients had respiratory complications (94) while the most common problems during the first month after injury were atelectasis and pneumonia (36%) (128). A longitudinal study assessed survival rates over the first 9 years after injury. They reported that in individuals with tetraplegia survival rates increased with years post injury and that survival rates were higher in ventilator independent persons compared to ventilator dependent (26). Although the mortality rate after an acute SCI decreased significantly during the last 40 years (78), a recent prospective mortality study including 28'000 persons with SCI in the U.S. reported that respiratory complications were the leading cause of death (28%) during the first year after injury and were ranked 3rd (18%) beyond the first year after injury (48). Respiratory complications during the first two years after injury decreased substantially over the last three decades, but there was no decrease in the chronic stage of an SCI (148). Thus, the time succeeding 2 years after injury is important for regular screening and prevention of pulmonary complications of persons with chronic SCI. Unfortunately little is known about prevention strategies of pulmonary complications and their effectiveness in subjects with SCI.

Respiratory function measurements in SCI

Accuracy of lung function measurement in subjects with SCI is very important, in order to answer the question whether they generally show decreases in lung volumes, flows and respiratory muscle strength due to lesion dependent paralysis (7, 97, 109). Therefore, Kelley et al. examined the degree to which the spirometry testing standards of the American Thoracic Society (ATS) were adhered to in a large cohort of subjects with SCI (89). This study showed that 83% of all tested subjects with SCI (n = 278) met the ATS acceptability standards and even 94% met the ATS reproducibility standards for lung function testing (89). Although a rather high percentage of subjects fulfilled able bodied standards, they adapted these standards for subjects with SCI in order to not provoke a positive selection bias. The exclusion of subjects could confound the assessment of the true effect of SCI on pulmonary function. This study and also a preliminary study of the same group (11) showed that particularly subjects with cervical, motor complete SCI were not able to meet ATS criteria (5). Therefore adaptations were made with respect to the minimum time needed for exhalation to measure forced vital capacity (FVC). The originally required 6 seconds of expiration time were not maintained and the end of test criteria was reduced to a minimum of a 0.5 s plateau

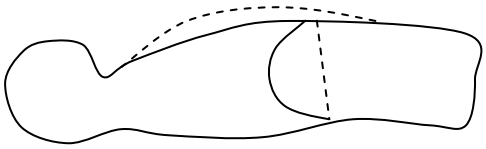
(11). Using these new criteria in subjects with SCI, the reproducibility of the results was now even higher (98%) and the acceptability increased to 94% of all subjects tested (89).

Depending on the level and completeness of the lesion, the respiratory function of subjects with SCI is affected to different extents, decreasing respiratory function with increasing lesion level (7, 96). Therefore, reference equations of able bodied individuals (127) can not be applied to subjects with SCI and have to include the lesion level. Lung function seems to change over time, showing strong increases during the first year after injury (17, 101) with further increases until 10 years after injury, but high decreases thereafter (150). Decreases in FVC beyond 10 years after injury seem to be much higher than the known loss in able bodied individuals due to increasing age (127, 150). This high decrease may arise due to rib cage stiffening especially in subjects without intercostal muscle activity (65, 116). Nevertheless, neither are lesion dependent reference equations, nor longitudinal lung function data after SCI known for this population. Regarding respiratory muscle strength, even less is known about lesion dependent differences and time-courses after SCI. Only one recently published study (109) assessed lesion dependent impairments in respiratory muscle pressure generating capacity - a measure of respiratory muscle strength - and showed that increasing lesion level also decreases maximal inspiratory muscle presssure generation (Pi_{max}) and maximal expiratory muscle pressure generation (Pe_{max}), while Pe_{max} was much more affected than Pi_{max} compared to able bodied reference values (16). Data of this study were assessed in patients between 1 month and 22 years after injury (109). Since lung function showed large changes especially early after injury, the same can be expected for respiratory muscle pressure generation and thus these data may not be very representative of all subjects or be easily compared with subjects at a certain time after injury. Longitudinal changes in respiratory muscle pressure generation after SCI have never been investigated in literature so far.

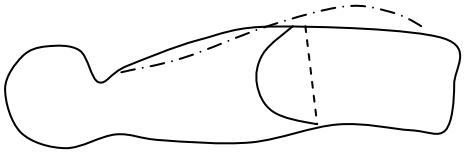
1.5 Respiratory mechanics in SCI

Respiratory muscle paralysis that occurs to different extents in subjects with SCI also alters respiratory mechanics (160). Changes in chest wall mechanics influence compliance of the whole respiratory system which may decrease breathing efficiency and especially impair coughing. A reduced mobility of the chest wall leads to rib cage stiffening during the chronic phase of SCI (116), which may in turn decrease lung volumes and thus also the ability to cough (22). Coughing is important, especially in subjects with tetraplegia, in order to clear secretion (24). Causes of changes in respiratory compliance after SCI are related to an increased abdominal compliance and a decrease in chest wall mobility. Decreases in chest wall mobility may occur due to chronically diminished thoracic excursions because of inspiratory muscle weakness. This in turn leads to stiffness of tendons, ligaments and

ankylosis in the joints of the rib cage which induces stiffness of the whole thoracic cage (53, 56). Changes in mobility of the chest wall and abdomen induce restrictive ventilatory impairments and a paradoxical breathing pattern in subjects with tetraplegia and high paraplegia (160). Due to paralyzed intercostal muscle function, the chest wall is drawn inward during inspiration and the highly compliant abdominal wall moves outward due to the absence of abdominal muscle function (Figure 4). Additionally, postural changes affect respiration of subjects with SCI to a much higher degree than in able bodied individuals and much more in persons with tetraplegia than in paraplegic individuals (29). While in able bodied persons FVC slightly decreases from erect to supine, FVC slightly increases in subjects with paraplegia and substantially increases in subjects with teraplegia by about 0.4 l, which may lay around 20% of FVC in subjects with tetraplegia (29, 54). This phenomenon occurs due to the disadvantageous position of the diaphragm, which in the sitting position is less pushed up by the abdominal content because of paralyzed abdominal muscles. Thus, in subjects with SCI the diaphragm has to operate at a disadvantageous force-length relationship (24).



Inspiration in able bodied individuals



Inspiration in spinal cord injured individuals

Figure 4: Effects of inspiration to the abdominal and thoracic wall in able bodied and tetraplegic individuals (paradoxical breathing pattern) — resting; ---- active; – · – · passive.

In the supine position, the gravitational force decreases abdominal compliance in tetraplegic subjects which causes an advantageous resting position of the diaphragm and thus increases lung volumes.

Respiratory mechanics in able bodied and tetraplegic individuals was intensively studied by Estenne & De Troyer since the early eighties (37-42, 53, 58). One of the most interesting and clinically relevant topics is expiratory muscle function and cough production in subjects with teraplegia which often has been described as fully passive due to expiratory muscle paralysis (139, 160). Estenne & De Troyer found that the clavicular portion of the pectoralis major muscle plays a major role during coughing and that coughing is an active rather than a passive process in subjects with tetraplegia (52). Consequently, they trained the clavicular portion of the pectoralis muscle in subjects with tetraplegia and found an increase in expiratory reserve volume and an improvement in expiratory muscle function (57). Further, they found that during the expiratory phase of coughing the diaphragm is active in subjects with abdominal

muscle paralysis and that the paradoxical expansion of the abdomen during coughing is induced by the action of the pectoralis major and not by the diaphragm (55).

1.6 Respiratory muscle training in SCI

The facts described in chapters 1.4 and 1.5 pointed out that the respiratory system of subjects with SCI is severely affected. Due to the lesion dependent loss of respiratory muscle innervation, the remaining active respiratory muscles have to accomplish the whole work of breathing. Thus, these muscles have to work at a higher relative intensity compared to able bodied individuals in daily life and especially during physical exercise tasks. There is some evidence that the diaphragm fatigues during physical exercise in subjects with tetraplegia (141) and that ventilatory muscle endurance can be enhanced by physical endurance exercise training in these patients (140). Fatigue of respiratory muscles may also impair cough capacity and therefore increase the risk for respiratory complications. Even though this hypothesis is not yet confirmed, several authors investigated different types of respiratory muscle training in subjects with SCI, aiming to increase pulmonary function and decrease the risk of respiratory complications (46, 69, 70, 95). The main findings of respiratory muscle training studies in subjects with SCI are summarized in two recent review papers (23, 153). The review written by van Houtte et al. included studies about all types of respiratory muscle training in SCI. Of the 23 papers that assessed effects of respiratory muscle training in SCI, only 6 were controlled trials and thus included in the review (57, 69, 84, 95, 100, 162). Unfortunately, a meta-analysis of these studies was not possible due to unreported data and heterogeneity in outcome variables (153). However, from the 6 trials included in the systematic review they finally concluded that respiratory muscle training showed tendencies to increase Pe_{max} and FVC and decrease residual volume (RV). Unfortunately, it was not possible to draw conclusions about the effects of respiratory muscle training on Pi_{max}, respiratory muscle endurance, quality of life, exercise performance and respiratory complications (153). Two of the six controlled studies investigated resistive inspiratory muscle training (95, 100), two others used a kind of inspiratory strength-endurance training (151, 162), and the other two investigated expiratory muscle training, one by resistive loading of respiratory muscles (69) and the other one by pectoralis muscle training (57). Thus, task specific effects of different respiratory muscle training methods still remain unclear. The other review written by Brooks et al. solely included studies about inspiratory muscle training in tetraplegic subjects (23). From the 40 articles retrieved, only three (46, 95, 100) met the inclusion criteria of randomized controlled trials and for similar causes as in the review of van Houtte et al. (153), a meta-analysis could not be performed and no overall effect could be confirmed. The various types and training regimes of the papers included in the systematic reviews clearly show that little evidence exists about effects of respiratory muscle training in

SCI, although there is some indication of positive influences in able bodied individuals. Interestingly, none of the reviewed studies used normocapnic hyperpnoea training.

1.7 Outline of the Thesis

Aim of the present studies

Respiration is an essential function in daily life of human beings. Since respiration is affected to different degrees in subjects with SCI, the optimal functioning of the remaining part of the respiratory system is vitally important to subjects with SCI. Detailed knowledge of lesion dependent impairments, trajectories of impairments and differences between able bodied subjects and individuals with para- or tetraplegia are important to know. Such knowledge should help to individualize interventions and thus improve primary and lifelong care of individuals with SCI. Improved respiratory function may lead to better physical functioning, improved quality of life and decreased pulmonary function and thus also decreases in health care costs. The main aims of this thesis therefore are to evaluate lesion dependent determinants of low respiratory function, differences in chest wall mobility between subjects with tetrapelgia and able bodied individuals and to investigate the effects of normocapnic hyperpnoea training in subjects with SCI in order to improve pulmonary function and exercise performance.

Some cross-sectional research has been performed about impairments in respiratory function but mostly in heterogeneous groups of individuals with chronic SCI (7, 96, 97, 109, 146). Nevertheless, none of these studies investigated lesion dependent determinants and trajectories of lung function and respiratory muscle strength in individuals with SCI over the whole range of lesion levels and at a consistent time post injury. Therefore **Chapter 2** evaluates respiratory function in SCI one year after discharge from inpatient rehabilitation and presents regression equations for lung function and respiratory muscle strength in subjects with motor complete and motor incomplete para- and tetraplegia separately. Further, it provides information about associations of lung function with respiratory muscle pressure generation in subjects with different levels of SCI.

Chapter 3 provides additional clinically relevant information about time-courses of lung function and respiratory muscle pressure generation during and one year after discharge from inpatient rehabilitation. The aim of this study was to compare time-courses of respiratory function between the different respiratory parameters as well as between different lesion level groups. Respiratory muscle endurance training by means of normocapnic hyperpnoea training improved respiratory muscle endurance and in some studies also physical endurance exercise performance in able bodied subjects (19, 20, 83, 106, 112, 143, 145, 149). Therefore, normocapnic hyperpnoea training may also be an interesting mean to improve respiratory function and physical exercise performance in subjects with SCI. Due to the lower amount of

respiratory muscle mass in subjects with SCI, normocapnic hyperpnoea training may probably not be performed at the same relative intensity level as in able bodied subjects. Since no study used normocapnic hyperpnoea training in individuals with SCI, **Chapter 4** presents a paper about the optimal intensity for normocapnic hyperpnoea training in subjects with para- and tetraplegia separately.

Wheelchair racing athletes with SCI use respiratory muscles concurrently for breathing and locomotion. Therefore normocapnic hyperpnoea training may have different effects on wheelchair racing performance compared to the ones of cycling in able bodied individuals. Thus, **Chapter 5** addresses the effects of normocapnic hyperpnoea training on wheelchair racing performance in athletes with SCI, by means of a 10 km time-trial. Further, effects on lung function and respiratory muscle pressure generation, respiratory muscle endurance and VO_{2peak} are assessed as well.

High blood lactate levels are produced during anaerobic exercise intensities as e.g. short distance wheelchair racing. Blood lactate elimination is enhanced using a previously loaded large muscle group for active recovery. Normocapnic hyperpnoea exercise is performed by respiratory muscles which mainly contain type I fibres, the main lactate consumers. Thus normocapnic hyperpnoea may be advantageous as a recovery strategy in order to preserve energy sources of the limb muscles. The aim of the study presented in **Chapter 6** is to investigate the impact of low intensity normocapnic hyperpnoea on blood lactate disappearance after exhaustive arm exercise in comparison to passive (rest) and active recovery (low intensity arm cranking) using the previously loaded muscle groups.

A decrease in rib cage mobility due to stiffening is a problem that affects respiratory function of subjects with chronic tetraplegia (53, 56) in addition to other problems discussed above. We hypothesize that respiratory muscle training may also help to increase rib cage mobility or decrease the process of stiffening. Nevertheless, a fast and easily applied method to measure rib cage mobility with a high level of reproducibility does not exist. Therefore we developed a new method using computed tomography and tested it's reproducibility in able bodied individuals and subjects with chronic tetraplegia. Intra-subject as well as intra- and inter-tester reproducibility of our new method to measure rib cage mobility are addressed in **Chapter 7**.

Chapter 8 describes differences in breathing mechanics between individuals with chronic, motor complete tetraplegia and matched able bodied subjects. The aim of this chapter is to evaluate differences in diaphragmatic movements and rib cage mobility between able bodied subjects and tetraplegic persons using the method described in chapter 7. Knowledge of such differences should help to quantify possible changes which may occur due to respiratory muscle training and thus improve knowledge about which training principle, amount and intensity is best for which SCI patient group.

In **Chapter 9** the findings of the chapters 2 to 8 are summarized and general conclusions are drawn. Further, the findings of this thesis are discussed and continuative research in the area of respiratory muscle training in subjects with SCI with implications for clinical practice is suggested.

1.8 Methods applied in this thesis

Lung function testing

Lung function measurement is a widely accepted, easy to perform and non-invasive clinical tool for the diagnosis and the monitoring of therapy effectiveness or the time-course of a disease. The individual is asked to perform different breathing maneuvers which consist of slow and forced maximal in- and expirations and some seconds of maximal voluntary hyperventilation. FVC is the change in volume of air in the lungs from complete inspiration to complete expiration. Forced expiratory volume in one second (FEV_1) is the volume of air exhaled in the first second of a forced expiration starting from full inspiration. FEV_1 often is expressed as % of FVC, also known as 'Tiffenau-Index'. A normal 'Tiffenau-Index' is around 80% whereas a low value provides some evidence of an obstructive impairment. In patients with restrictive impairments (e.g. subjects with tetraplegia), the 'Tiffenau-Index' may be normal or increased. Forced inspiratory volume in one second (FIV_1) is the volume of air inhaled in the first second of a forced inspiration starting from full expiration. Peak expiratory flow (PEF) is the greatest flow that can be sustained on forced expiration starting from full inflation of the lungs and is measured in litres per second. PEF may be lowered due to weakness of expiratory muscles, thorax deformities and emphysema. Peak inspiratory flow (PIF) is the greatest flow that can be sustained on forced inspiration starting from full expiration of the lungs. Lung volumes are illustrated graphically on Figure 5.1. Maximal voluntary ventilation (MVV) is a measure of maximal ventilatory capacity, i.e. maximal voluntary hyperpnoea. MVV is usually measured during 12 or 15 seconds and calculated as maximal breathing capacity over one minute, expressed in l/min. Tidal volume (V_T) represents the volume one in- and exhales during normal quiet breathing at rest. Functional residual capacity (FRC) represents the end expiratory lung volume after a normal 'passive' expiration. At FRC all respiratory muscles are in a more or less relaxed state, i.e. there is equilibrium between outward pulling forces of the thorax and inward pulling forces of the lungs. FRC can be measured by bodyplethysmography (see below) as intra-thoracic gas volume (IGV). Measurement of IGV constitutes the basis for calculation of RV and total lung capacity (TLC). Expiratory reserve volume (ERV) is the volume that can be exhaled from FRC, using active expiratory muscles. RV is the volume that fills the lungs and airways after total expiration, i.e. FRC minus ERV. TLC represents the maximal volume that the lung and airways can contain, i.e. RV + FVC. These volumes are shown in Figure 5.2.

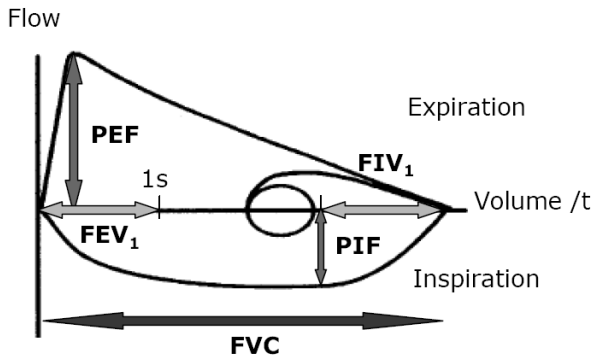


Figure 5.1: Flow-volume curve showing parameters of lung function testing.

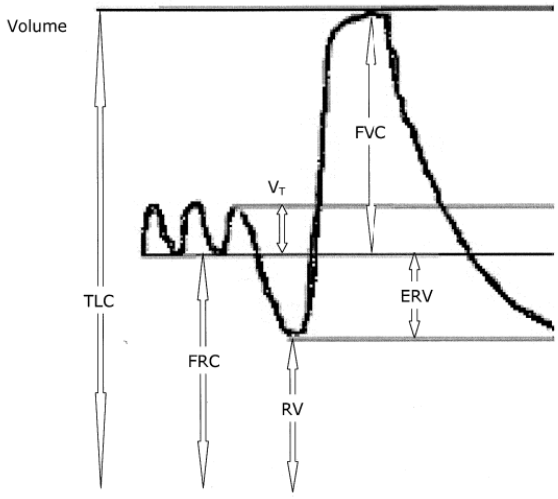


Figure 5.2: Volume curve showing different volumes of quiet breathing and maximal in- and expiration.

Quality of measurements

Normal lung function parameters as shown in Figure 5.1 are determined by spirometry using a mouthpiece with a calibrated turbine. Lung function testing is highly dependent on the effort put in by the subject and the quality of the tester. At the end of the maneuvers there should be no volume displacement over a period of 6 seconds in able bodied subjects (5). Lung function testing that does not fulfill this quality feature are frequent and mainly dependent on the tester (73). A further quality standard of lung function testing is to perform at least three consecutive repetitions of all maneuvers where values are within a range of 5% (127).

The concept of reference equations

FVC and consequently all other lung function parameters mainly depend on gender, height and age. Thus, reference equations for FVC, FEV_1 and PEF containing these factors were created (127). It is an ongoing debate how accurate these reference equations are, since many other factors such as body weight, smoking or diseases like diabetes mellitus may influence lung function as well (13, 120). Nevertheless, the European Respiratory Society accepted and published the reference equations of Quanier et al. as European standard measures (127). Many others published reference equations for different age- and ethnic groups (1, 85, 107, 125). Unfortunately, reference equations are only available for FVC, FEV_1, PEF, ERV, IGV and TLC, but not for FIV_1 and PIF (127).

Bodyplethysmography

Today's 'gold standard' of lung function measurement is bodyplethysmography. In addition to normal spirometry, IGV and airway resistances can be determined by bodyplethysmography. The measurement principle of bodyplethysmography is based on the 'Boyle-Mariotte-Law' which says that under isothermic conditions, pressure times volume is constant (P x V = const.). A Bodyplethysmograph is a hermetically sealed cabin of 700-1000 l into which the subject is placed in. The changes of pressure in the cabin are proportional to the alveolar pressure. A pneumotachograph measures changes in mouth pressure (i.e. alveolar pressure) and cabin pressure during quiet and occluded breathing to determine IGV (i.e. FRC) and breathing resistance. A disadvantage of IGV measurement is that the content of the gastric bladder is measured as well which often produces 'false positive' TLC and RV data. This has to be taken into account, especially for follow-up measurements.

Respiratory muscle pressure testing

The most simple and most common approach of respiratory muscle pressure testing is to measure Pi_{max} and Pe_{max} at the mouth when the subject makes maximal efforts against a closed airway (129.) The preferred technique to measure Pi_{max} and Pe_{max} is the one described by Black and Hyatt (16). They also defined normal values for Pi_{max} and Pe_{max} that depend on sex and age (16). The important thing about measuring Pi_{max} and Pe_{max} is that the mouthpiece of the measurement device has a small air-leak that prevents glottis closure, to avoid that facial muscles are able to contribute to expiratory pressure. In order to generate Pi_{max}, the subject exhales to RV and makes a maximal powerful inspiratory effort. To generate Pe_{max} the subject inhales to TLC and makes a maximal expiratory effort. Both, Pi_{max} and Pe_{max} should be sustained for a few seconds. The basic determinants of respiratory muscle pressure - the common measures of respiratory muscle strength - are similar to those of skeletal muscle strength and consist of: (129)

1. The resting length of the muscle prior to contraction (force-length relationship) (67)
2. Whether or not the muscle is allowed to shorten during contraction
   (force-velocity relationship) (81)
3. The strength and frequency of stimulation (force-frequency relationship)
4. The integrity of the contractile apparatus

Therefore, the muscle length at which respiratory muscle strength is measured plays an important role for the interpretation of the data. Especially in subjects with obstructive or restrictive breathing disorders (e.g. tetraplegics), muscles may not be at their optimal length to perform maximal efforts. Even if Pi_{max} and Pe_{max} are normally measured at RV and TLC, one

has to be aware of the fact that the elastic recoil of the lungs and the chest wall is measured as well. Especially Pi_{max} is highly affected by pulmonary recoil forces and thus Pi_{max} measured from RV is overestimated by about 30% in healthy able bodied individuals (129). Measurement from FRC would resolve this problem, but the disadvantage that FRC is less reproducible than TLC and RV equals the advantage of measurement from FRC. Learning effects of respiratory muscle strength maneuvers seem to be higher than those for lung function measurement (154, 157). Therefore oftentimes, more than three measurements have to be performed to get three values within 5%. The higher learning effects of Pi_{max} and Pe_{max} maneuvers may occur because these maneuvers are more difficult to perform for the subjects than lung function maneuvers. Therefore, some additional and easier to perform tests are recommended to measure inspiratory (sniff test) (114) and expiratory (cough test) (10) muscle strength. The sniff maneuver is an alternative to Pi_{max} that is more natural and easier to perform for most subjects. A sniff maneuver is usually measured from FRC, while the subject performs short and sharp sniffs through the nose and the mouth is occluded (79). Sniff nasal inspiratory pressure (SNIP) is measured in one nostril which is occluded by the device while the other nostril is open. The SNIP test was shown to be reliable and is suggested as an additional test for those subjects who show problems in performing Pi_{max} maneuvers (80). The cough test consists of performing a maximal cough while measuring the peak flow during this maneuver. Since coughing is a common task, most people report fewer problems while performing a maximal cough compared to a Pe_{max} maneuver. The cough test may especially be helpful for testing individuals with diseases that affect expiratory muscle function. Causes of weakness in respiratory muscle pressure generating capacity may be neuromuscular disease, mechanical, metabolic and nutritional factors or reduction of neural drive (129). Testing of respiratory muscle pressures in addition to lung function measurement seems to be highly important in clinical practice, since e.g. severe respiratory muscle weakness alone can lead to respiratory failure (21).

Normocapnic hyperpnoea training

In order to perform isolated endurance training for the respiratory muscles, normocapnic hyperpnoea training may be applied. During normocapnic hyperpnoea training, intensive isolated hyperventilation is performed as exercise task. Using a specific normocapnic hyperpnoea training device, voluntary, non-resistive hyperpnoea with either added CO_2 or partial re-breathing is performed while minute ventilation, i.e. breathing volume and frequency, has to be held constant. The amount of CO_2 that one re-breathes has to be adjusted so that end tidal CO_2 stays around individual resting conditions. Because of the complicated equipment needed to perform normocapnic hyperpnoea training, it was not possible to perform such training in a home setting initially. Since the year 2001, a commercially available mobile normocapnic hyperpnoea training device, called ‘Spiro Tiger’ is available

from idiag AG (idiag AG, Müllistr. 18, CH-8320 Fehraltorf, Switzerland; www.idiag.ch). This mobile device consists of a hand held unit with a respiratory pouch and a base station (Figure 6).

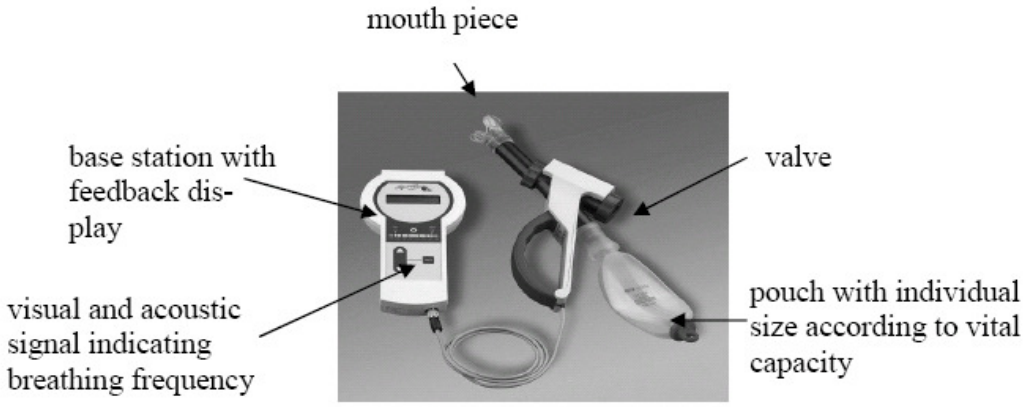


Figure 6: The Spiro Tiger device; reprinted with permission of idiag AG

The size of the pouch is available in different sizes and should be approximately 50% of FVC. The first part of exhaled air fills the pouch (2/3 to 3/4 of exhaled air) and the rest is expired through the valve. Breathing frequency is adjusted so that normocapnic hyperpnoea training is performed between 60 and 70% MVV in able bodied subjects. A visual and acoustic signal indicates the breathing frequency on the base station which can be individually programmed with the size of the pouch, the target breathing frequency and the training time. The electronic device registers the opening time of the valve and thus calculates tidal volume while controlling for the correct breathing frequency. Finally, the feedback display provides information about minute ventilation and whether the breathing frequency is too high or too low. After one or two initial training sessions, where end tidal CO_2 partial pressure should be controlled by a cardio-respiratory measurement device, normocapnic hyperpnoea training can be performed independently.

References

1. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis* 144: 1202-1218, 1991.
2. NHLBI Workshop summary. Respiratory muscle fatigue. Report of the Respiratory Muscle Fatigue Workshop Group. *Am Rev Respir Dis* 142: 474-480, 1990.
3. Spinal cord injury facts and figures at a glance. August 2004. *J Spinal Cord Med* 27 Suppl 1: S139-140, 2004.
4. Spinal cord injury. Facts and figures at a glance. *J Spinal Cord Med* 28: 379-380, 2005.
5. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 152: 1107-1136, 1995.
6. **Alander DH, Andreychik DA, and Stauffer ES**. Early outcome in cervical spinal cord injured patients older than 50 years of age. *Spine* 19: 2299-2301, 1994.

7. **Almenoff PL, Spungen AM, Lesser M, and Baumann WA**. Pulmonary function survey in spinal cord injury: influences of smoking and level and completeness of injury. *Lung* 173: 297-306, 1995.
8. **Alvarez SE, Peterson M, and Lunsford BR**. Respiratory treatment of the adult patient with spinal cord injury. *Phys Ther* 61: 1737-1745, 1981.
9. **Anke A, Aksnes AK, Stanghelle JK, and Hjeltnes N**. Lung volumes in tetraplegic patients according to cervical spinal cord injury level. *Scand J Rehabil Med* 25: 73-77, 1993.
10. **Arora NS, and Gal TJ**. Cough dynamics during progressive expiratory muscle weakness in healthy curarized subjects. *J Appl Physiol* 51: 494-498, 1981.
11. **Ashba J, Garshick E, Tun C, Lieberman SL, Polakoff D, Blanchard J, and Brown R**. Spirometry - Acceptability and Reproducibility in Spinal Cord injured Subjects. *J Am Parapl Soc* 16: 197-203, 1993.
12. **ASIA**. *International Standards for Neurological Classification of SCI*. Chicago: American Spinal Injury Association, 2000.
13. **Becklake MR**. Concepts of normality applied to the measurement of lung function. *Am J Med* 80: 1158-1164, 1986.
14. **Belman MJ, and Gaesser GA**. Ventilatory muscle training in the elderly. *J Appl Physiol* 64: 899-905, 1988.
15. **Belman MJ, and Shadmehr R**. Targeted resistive ventilatory muscle training in chronic obstructive pulmonary disease. *J Appl Physiol* 65: 2726-2735, 1988.
16. **Black LF, and Hyatt RE**. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 99: 696-702, 1969.
17. **Bluechardt MH, Wiens M, Thomas SG, and Plyley MJ**. Repeated measurements of pulmonary function following spinal cord injury. *Paraplegia* 30: 768-774, 1992.
18. **Boutellier U**. Respiratory muscle fitness and exercise endurance in healthy humans. *Med Sci Sports Exerc* 30: 1169-1172, 1998.
19. **Boutellier U, Buchel R, Kundert A, and Spengler C**. The respiratory system as an exercise limiting factor in normal trained subjects. *Eur J Appl Physiol Occup Physiol* 65: 347-353, 1992.
20. **Boutellier U, and Piwko P**. The respiratory system as an exercise limiting factor in normal sedentary subjects. *Eur J Appl Physiol Occup Physiol* 64: 145-152, 1992.
21. **Braun NM, Arora NS, and Rochester DF**. Respiratory muscle and pulmonary function in polymyositis and other proximal myopathies. *Thorax* 38: 616-623, 1983.
22. **Braun SR, Giovannoni R, and O'Connor M**. Improving the cough in patients with spinal cord injury. *Am J Phys Med* 63: 1-10, 1984.
23. **Brooks D, O'Brien K, Geddes EL, Crowe J, and Reid WD**. Is inspiratory muscle training effective for individuals with cervical spinal cord injury? A qualitative systematic review. *Clin Rehabil* 19: 237-246, 2005.
24. **Brown R, DiMarco AF, Hoit JD, and Garshick E**. Respiratory dysfunction and management in spinal cord injury. *Respir Care* 51: 853-868;discussion 869-870, 2006.
25. **Cardenas DD, Hoffman JM, Kirshblum S, and McKinley W**. Etiology and incidence of rehospitalization after traumatic spinal cord injury: a multicenter analysis. *Arch Phys Med Rehabil* 85: 1757-1763, 2004.
26. **Carter RE**. Respiratory aspects of spinal cord injury management. *Paraplegia* 25: 262-266, 1987.
27. **Casaburi R**. Principles of exercise training. *Chest* 101: 263S-267S, 1992.
28. **Celani MG, Spizzichino L, Ricci S, Zampolini M, and Franceschini M**. Spinal cord injury in Italy: A multicenter retrospective study. *Arch Phys Med Rehabil* 82: 589-596, 2001.
29. **Chen CF, Lien IN, and Wu MC**. Respiratory function in patients with spinal cord injuries: effects of posture. *Paraplegia* 28: 81-86, 1990.
30. **Cheng YJ, Macera CA, Addy CL, Sy FS, Wieland D, and Blair SN**. Effects of physical activity on exercise tests and respiratory function. *Br J Sports Med* 37: 521-528, 2003.
31. **Chevrolet JC, Tschopp JM, Blanc Y, Rochat T, and Junod AF**. Alterations in inspiratory and leg muscle force and recovery pattern after a marathon. *Med Sci Sports Exerc* 25: 501-507, 1993.
32. **Coast JR, Clifford PS, Henrich TW, Stray-Gundersen J, and Johnson RL, Jr.** Maximal inspiratory pressure following maximal exercise in trained and untrained subjects. *Med Sci Sports Exerc* 22: 811-815, 1990.
33. **Dalyan M, Sherman A, and Cardenas DD**. Factors associated with contractures in acute spinal cord injury. *Spinal Cord* 36: 405-408, 1998.

34. **Daud O, Sett P, Burr RG, and Silver JR**. The relationship of heterotopic ossification to passive movements in paraplegic patients. *Disab Rehabil* 15: 114-118, 1993.
35. **de Groot S, Dallmeijer AJ, Post MW, van Asbeck FW, Nene AV, Angenot EL, and van der Woude LH**. Demographics of the Dutch multicenter prospective cohort study 'Restoration of mobility in spinal cord injury rehabilitation'. *Spinal Cord* 44: 668-675, 2006.
36. **de Jong W, van Aalderen WM, Kraan J, Koeter GH, and van der Schans CP**. Inspiratory muscle training in patients with cystic fibrosis. *Respir Med* 95: 31-36, 2001.
37. **De Troyer A**. The mechanism of the inspiratory expansion of the rib cage. *J Lab Clin Med* 114: 97-104, 1989.
38. **De Troyer A, and Estenne M**. Chest wall motion in paraplegic subjects. *Am Rev Respir Dis* 141: 332-336, 1990.
39. **De Troyer A, and Estenne M**. The expiratory muscles in tetraplegia. *Paraplegia* 29: 359-363, 1991.
40. **De Troyer A, and Estenne M**. Functional anatomy of the respiratory muscles. *Clin Chest Med* 9: 175-193, 1988.
41. **De Troyer A, and Heilporn A**. Respiratory mechanics in quadriplegia. The respiratory function of the intercostal muscles. *Am Rev Respir Dis* 122: 591-600, 1980.
42. **De Troyer A, Sampson M, Sigrist S, and Macklem PT**. The diaphragm: two muscles. *Science* 213: 237-238, 1981.
43. **Dekhuijzen PN, Hopman MT, Binkhorst RA, and Folgering HT**. Target-flow inspiratory muscle training: breathing patterns and metabolic costs. *Int J Rehabil Res* 14: 293-301, 1991.
44. **Dempsey JA**. J.B. Wolffe memorial lecture. Is the lung built for exercise? *Med Sci Sports Exerc* 18: 143-155, 1986.
45. **Dempsey JA, and Babcock MA**. An integrative view of limitations to muscular performance. *Adv Exp Med Biol* 384: 393-399, 1995.
46. **Derrickson J, Cielsa N, Simpson N, and Imle PC**. A comparison of two breathing exercise programs for patients with quadriplegia. *Phys Ther* 72: 763-769, 1992.
47. **DeVivo MJ, Kartus PL, Stover SL, Rutt RD, and Fine PR**. Cause of death for patients with spinal cord injuries. *Arch Intern Med* 149: 1761-1766, 1989.
48. **DeVivo MJ, Krause JS, and Lammertse DP**. Recent trends in mortality and causes of death among persons with spinal cord injury. *Arch Phys Med Rehabil* 80: 1411-1419, 1999.
49. **di Prampero PE, and Ferretti G**. Factors limiting maximal oxygen consumption in humans. *Respir Physiol* 80: 113-127, 1990.
50. **Eberhard S**. Statistik der stationären Behandlungen bei Querschnittlähmung in der Schweiz. *Managed Care* 2: 4-9, 2004.
51. **Enright SJ, Unnithan VB, Heward C, Withnall L, and Davies DH**. Effect of high-intensity inspiratory muscle training on lung volumes, diaphragm thickness, and exercise capacity in subjects who are healthy. *Phys Ther* 86: 345-354, 2006.
52. **Estenne M, and De Troyer A**. Cough in tetraplegic subjects: an active process. *Ann Intern Med* 112: 22-28, 1990.
53. **Estenne M, and De Troyer A**. The effects of tetraplegia on chest wall statics. *Am Rev Respir Dis* 134: 121-124, 1986.
54. **Estenne M, and De Troyer A**. Mechanism of the postural dependence of vital capacity in tetraplegic subjects. *Am Rev Respir Dis* 135: 367-371, 1987.
55. **Estenne M, and Gorini M**. Action of the diaphragm during cough in tetraplegic subjects. *J Appl Physiol* 72: 1074-1080, 1992.
56. **Estenne M, Heilporn A, Delhez L, Yernault JC, and De Troyer A**. Chest wall stiffness in patients with chronic respiratory muscle weakness. *Am Rev Respir Dis* 128: 1002-1007, 1983.
57. **Estenne M, Knoop C, Vanvaerenbergh J, Heilporn A, and De Troyer A**. The effect of pectoralis muscle training in tetraplegic subjects. *Am Rev Respir Dis* 139: 1218-1222, 1989.
58. **Estenne M, Yernault JC, and De Troyer A**. Rib cage and diaphragm-abdomen compliance in humans: effects of age and posture. *J Appl Physiol* 59: 1842-1848, 1985.
59. **Fairbarn MS, Coutts KC, Pardy RL, and McKenzie DC**. Improved respiratory muscle endurance of highly trained cyclists and the effects on maximal exercise performance. *Int J Sports Med* 12: 66-70, 1991.
60. **Felleiter P, Reinbott S, Michel F, and Baumberger M**. Das Traumatische Querschnittsyndrom. *Schweiz Med Forum* 4: 1166-1172, 2004.

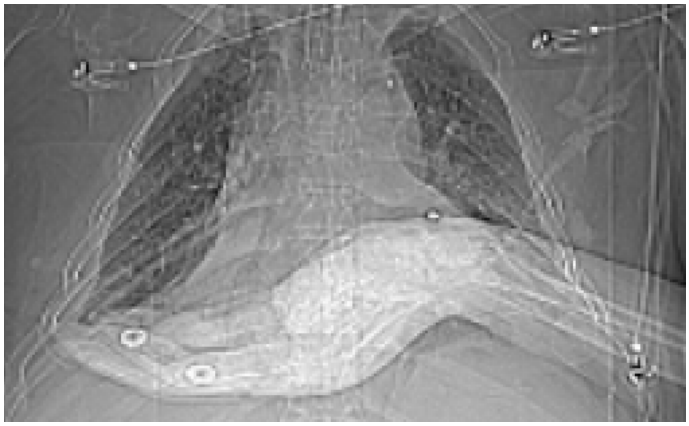
61. **Fishburn MJ, Marino RJ, and Ditunno JF, Jr.** Atelectasis and pneumonia in acute spinal cord injury. *Arch Phys Med Rehabil* 71: 197-200, 1990.
62. **Fitting JW**. Respiratory muscle fatigue limiting physical exercise? *Eur Respir J* 4: 103-108, 1991.
63. **Garber SL, Rintala DH, Hart KA, and Fuhrer MJ**. Pressure ulcer risk in spinal cord injury: predictors of ulcer status over 3 years. *Arch Phys Med Rehabil* 81: 465-471, 2000.
64. **Gething AD, Williams M, and Davies B**. Inspiratory resistive loading improves cycling capacity: a placebo controlled trial. *Br J Sports Med* 38: 730-736, 2004.
65. **Goldman JM, Williams SJ, and Denison DM**. The rib cage and abdominal components of respiratory system compliance in tetraplegic patients. *Eur Respir J* 1: 242-247, 1988.
66. **Goldstein RS**. Pulmonary rehabilitation in chronic respiratory insufficiency. 3. Ventilatory muscle training. *Thorax* 48: 1025-1033, 1993.
67. **Gordon AM, Huxley AF, and Julian FJ**. The variation in isometric tension with sarcomere length in vertebrate muscle fibres. *J Physiol* 184: 170-192, 1966.
68. **Gosselink R, Wagenaar RC, and Decramer M**. Reliability of a commercially available threshold loading device in healthy subjects and in patients with chronic obstructive pulmonary disease. *Thorax* 51: 601-605, 1996.
69. **Gounden P**. Progressive resistive loading on accessory expiratory muscles in tetraplegia. *Fisioterapie* 46: 4-16, 1990.
70. **Gross D, Ladd HW, Riley EJ, Macklem PT, and Grassino A**. The effect of training on strength and endurance of the diaphragm in quadriplegia. *Am J Med* 68: 27-35, 1980.
71. **Guenette JA, Martens AM, Lee AL, Tyler GD, Richards JC, Foster GE, Warburton DE, and Sheel AW**. Variable effects of respiratory muscle training on cycle exercise performance in men and women. *Appl Physiol Nutr Metab* 31: 159-166, 2006.
72. **Hanel B, and Secher NH**. Maximal oxygen uptake and work capacity after inspiratory muscle training: A controlled study. *J Sports Sci* 9: 43-52, 1991.
73. **Hankinson JL**. Office spirometry: does poor quality render it impractical? *Chest* 116: 276-277, 1999.
74. **Harms CA, Babcock MA, McClaran SR, Pegelow DF, Nickele GA, Nelson WB, and Dempsey JA**. Respiratory muscle work compromises leg blood flow during maximal exercise. *J Appl Physiol* 82: 1573-1583, 1997.
75. **Harms CA, Wetter TJ, McClaran SR, Pegelow DF, Nickele GA, Nelson WB, Hanson P, and Dempsey JA**. Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. *J Appl Physiol* 85: 609-618, 1998.
76. **Harms CA, Wetter TJ, St Croix CM, Pegelow DF, and Dempsey JA**. Effects of respiratory muscle work on exercise performance. *J Appl Physiol* 89: 131-138, 2000.
77. **Hart C, and Williams E**. Epidemiology of spinal cord injuries: a reflection of changes in South African society. *Paraplegia* 32: 709-714, 1994.
78. **Hartkopp A, Bronnum-Hansen H, Seidenschnur AM, and Biering-Sorensen F**. Survival and cause of death after traumatic spinal cord injury. A long-term epidemiological survey from Denmark. *Spinal Cord* 35: 76-85, 1997.
79. **Heritier F, Perret C, and Fitting JW**. Esophageal and mouth pressure during sniffs with and without nasal occlusion. *Respir Physiol* 86: 305-313, 1991.
80. **Heritier F, Rahm F, Pasche P, and Fitting JW**. Sniff nasal inspiratory pressure. A noninvasive assessment of inspiratory muscle strength. *Am J Respir Crit Care Med* 150: 1678-1683, 1994.
81. **Hill aV**. The heat of shortening and the dynamic constants of muscle. *Proc Royal Soc London, Serie B* 126: 136-195, 1938.
82. **Hill NS, Jacoby C, and Farber HW**. Effect of an endurance triathlon on pulmonary function. *Med Sci Sports Exerc*23: 1260-1264, 1991.
83. **Holm P, Sattler A, and Fregosi RF**. Endurance training of respiratory muscles improves cycling performance in fit young cyclists. *BMC Physiol* 4: 9, 2004.
84. **Huldtgren AC, Fugl-Meyer AR, Jonasson E, and Bake B**. Ventilatory dysfunction and respiratory rehabilitation in post-traumatic quadriplegia. *Eur J Respir Dis* 61: 347-356, 1980.
85. **Islam MS, and Ulmer WT**. [Reference values in ventilatory lung function]. *Prax Klin Pneumol* 37: 9-14, 1983.
86. **Johnson BD, Babcock MA, Suman OE, and Dempsey JA**. Exercise induced diaphragmatic fatigue in healthy humans. *J Physiol* 460: 385-405, 1993.
87. **Jordanoglou J**. Vector analysis of rib movement. *Respir Physiol* 10: 109-120, 1970.

88. **Keens TG, Krastins IR, Wannamaker EM, Levison H, Crozier DN, and Bryan AC**. Ventilatory muscle endurance training in normal subjects and patients with cystic fibrosis. *Am Rev Respir Dis* 116: 853-860, 1977.
89. **Kelley A, Garshick E, Gross ER, Lieberman SL, Tun CG, and Brown R**. Spirometry testing standards in spinal cord injury. *Chest* 123: 725-730, 2003.
90. **Klefbeck B, and Hamrah Nedjad J**. Effect of inspiratory muscle training in patients with multiple sclerosis. *Arch Phys Med Rehabil* 84: 994-999, 2003.
91. **Koessler W, Wanke T, Winkler G, Nader A, Toifl K, Kurz H, and Zwick H**. 2 Years' experience with inspiratory muscle training in patients with neuromuscular disorders. *Chest* 120: 765-769, 2001.
92. **Kohl J, Koller EA, Brandenberger M, Cardenas M, and Boutellier U**. Effect of exercise-induced hyperventilation on airway resistance and cycling endurance. *Eur J Appl Physiol Occup Physiol* 75: 305-311, 1997.
93. **Leith DE, and Bradley M**. Ventilatory muscle strength and endurance training. *J Appl Physiol* 41: 508-516, 1976.
94. **Lemons VR, and Wagner FC, Jr.** Respiratory complications after cervical spinal cord injury. *Spine* 19: 2315-2320, 1994.
95. **Liaw MY, Lin MC, Cheng PT, Wong MK, and Tang FT**. Resistive inspiratory muscle training: its effectiveness in patients with acute complete cervical cord injury. *Arch Phys Med Rehabil* 81: 752-756, 2000.
96. **Linn WS, Adkins RH, Gong H, Jr., and Waters RL**. Pulmonary function in chronic spinal cord injury: a cross-sectional survey of 222 southern California adult outpatients. *Arch Phys Med Rehabil* 81: 757-763, 2000.
97. **Linn WS, Spungen AM, Gong H, Adkins RH, Baumann WA, and Waters RL**. Forced vital capacity in two large outpatient populations with chronic spinal cord injury. *Spinal Cord* 39: 263-268, 2001.
98. **Loke J, Mahler DA, and Virgulto JA**. Respiratory muscle fatigue after marathon running. *J Appl Physiol* 52: 821-824, 1982.
99. **Lomax ME, and McConnell AK**. Inspiratory muscle fatigue in swimmers after a single 200 m swim. *J Sports Sci* 21: 659-664, 2003.
100. **Loveridge B, Badour M, and Dubo H**. Ventilatory muscle endurance training in quadripegia: Effects on breathing pattern. *Paraplegia* 27: 329-339, 1989.
101. **Loveridge B, Sanii R, and Dubo HI**. Breathing pattern adjustments during the first year following cervical spinal cord injury. *Paraplegia* 30: 479-488, 1992.
102. **Lucke KT**. Pulmonary management following acute SCI. *J Neurosci Nurs* 30: 91-104, 1998.
103. **Mador MJ, and Acevedo FA**. Effect of respiratory muscle fatigue on subsequent exercice performance. *J Appl Physiol* 70: 2059-2065, 1991.
104. **Mador MJ, Magalang UJ, Rodis A, and Kufel TJ**. Diaphragmatic fatigue after exercise in healthy human subjects. *Am Rev Respir Dis* 148: 1571-1575, 1993.
105. **Markov G, Orler R, and Boutellier U**. Respiratory training, hypoxic ventilatory response and acute mountain sickness. *Respir Physiol* 105: 179-186, 1996.
106. **Markov G, Spengler CM, Knopfli-Lenzin C, Stuessi C, and Boutellier U**. Respiratory muscle training increases cycling endurance without affecting cardiovascular responses to exercise. *Eur J Appl Physiol* 85: 233-239, 2001.
107. **Marsh S, Aldington S, Williams MV, Weatherall M, Robiony-Rogers D, Jones D, and Beasley R**. Pulmonary function testing in New Zealand: the use and importance of reference ranges. *Respirology (Carlton, Vic)* 12: 367-374, 2007.
108. **Martin B, Heintzelman M, and Chen HI**. Exercise performance after ventilatory work. *J Appl Physiol* 52: 1581-1585, 1982.
109. **Mateus SR, Beraldo PS, and Horan TA**. Maximal static mouth respiratory pressure in spinal cord injured patients: correlation with motor level. *Spinal Cord* 45: 569-575, 2007.
110. **McConnell AK, Caine MP, and Sharpe GR**. Inspiratory muscle fatigue following running to volitional fatigue: the influence of baseline strength. *Int J Sports Med* 18: 169-173, 1997.
111. **McConnell AK, and Romer LM**. Respiratory muscle training in healthy humans: resolving the controversy. *Int J Sports Med* 25: 284-293, 2004.
112. **McMahon ME, Boutellier U, Smith RM, and Spengler CM**. Hyperpnoea training attenuates peripheral chemosensitivity and improves cycling endurance. *J Exp Biol* 205: 3937-3943, 2002.

113. **Middleton JW, Lim K, Taylor L, Soden R, and Rutkowski S**. Patterns of morbidity and rehospitalisation following spinal cord injury. *Spinal Cord* 42: 359-367, 2004.
114. **Miller JM, Moxham J, and Green M**. The maximal sniff in the assessment of diaphragm function in man. *Clin Sci (Lond)* 69: 91-96, 1985.
115. **Morgan DW, Kohrt WM, Bates BJ, and Skinner JS**. Effects of respiratory muscle endurance training on ventilatory and endurance performance of moderately trained cyclists. *Int J Sports Med* 8: 88-93, 1987.
116. **Morgan MD, and De Troyer A**. The individuality of chest wall motion in tetraplegia. *Bull Eur Physiopathol Respir* 20: 547-552, 1984.
117. **Noreau L, Proulx P, Gagnon L, Drolet M, and Laramee MT**. Secondary impairments after spinal cord injury: a population-based study. *Am J Phys Med Rehabil / Assoc Acad Physiatr* 79: 526-535, 2000.
118. **Noreau L, and Shephard RJ**. Spinal cord injury, exercise and quality of life. *Sports Med* 20: 226-250, 1995.
119. **O'Connor RJ, and Murray PC**. Review of spinal cord injuries in Ireland. *Spinal Cord* 44: 445-448, 2006.
120. **Ostrowski S, and Barud W**. Factors influencing lung function: are the predicted values for spirometry reliable enough? *J Physiol Pharmacol* 57 Suppl 4: 263-271, 2006.
121. **Ouellet Y, Poh SC, and Becklake MR**. Circulatory factors limiting maximal aerobic exercise capacity. *J Appl Physiol* 27: 874-880, 1969.
122. **Padula CA, and Yeaw E**. Inspiratory muscle training: integrative review. *Res Theory Nursing Pract* 20: 291-304, 2006.
123. **Pardy RL, Reid WD, and Belman MJ**. Respiratory muscle training. *Clin Chest Med* 9: 287-296, 1988.
124. **Perret C, Spengler CM, Egger G, and Boutellier U**. Influence of endurance exercise on respiratory muscle performance. *Med Sci Sports Exerc* 32: 2052-2058, 2000.
125. **Piccioni P, Borraccino A, Forneris MP, Migliore E, Carena C, Bignamini E, Fassio S, Cordola G, Arossa W, and Bugiani M**. Reference values of Forced Expiratory Volumes and pulmonary flows in 3-6 year children: a cross-sectional study. *Respir Res* 8: 14, 2007.
126. **Powers SK, Coombes J, and Demirel H**. Exercise training-induced changes in respiratory muscles. *Sports Med* 24: 120-131, 1997.
127. **Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, and Yernault JC**. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 16: 5-40, 1993.
128. **Reines HD, and Harris RC**. Pulmonary complications of acute spinal cord injuries. *Neurosurgery* 21: 193-196, 1987.
129. **Rochester DF**. Tests of respiratory muscle function. *Clin Chest Med* 9: 249-261, 1988.
130. **Romer LM, and McConnell AK**. Specificity and reversibility of inspiratory muscle training. *Med Sci Sports Exerc* 35: 237-244, 2003.
131. **Romer LM, McConnell AK, and Jones DA**. Effects of inspiratory muscle training on time-trial performance in trained cyclists. *J Sports Sci* 20: 547-562, 2002.
132. **Romer LM, McConnell AK, and Jones DA**. Inspiratory muscle fatigue in trained cyclists: effects of inspiratory muscle training. *Med Sci Sports Exerc* 34: 785-792, 2002.
133. **Ronen J, Itzkovich M, Bluvshtein V, Thaleisnik M, Goldin D, Gelernter I, David R, Gepstein R, and Catz A**. Length of stay in hospital following spinal cord lesions in Israel. *Spinal Cord* 42: 353-358, 2004.
134. **Roth EJ, Lu A, Primack S, Oken J, Nusshaum S, Berkowitz M, and Powley S**. Ventilatory function in cervical and high thoracic spinal cord injury. Relationship to level of injury and tone. *Am J Phys Med Rehabil / Assoc Acad Physiatr* 76: 262-267, 1997.
135. **Schmitt J, Midha M, and McKenzie N**. Medical complications of spinal cord disease. *Neurol Clin* 9: 779-795, 1991.
136. **Schonherr MC, Groothoff JW, Mulder GA, and Eisma WH**. Rehabilitation of patients with spinal cord lesions in The Netherlands: an epidemiological study. *Spinal Cord* 34: 679-683, 1996.
137. **Sheel AW**. Respiratory muscle training in healthy individuals: physiological rationale and implications for exercise performance. *Sports Med* 32: 567-581, 2002.

138. **Sheel AW, Derchak PA, Morgan BJ, Pegelow DF, Jacques AJ, and Dempsey JA**. Fatiguing inspiratory muscle work causes reflex reduction in resting leg blood flow in humans. *J Physiol* 537: 277-289, 2001.
139. **Siebens AA, Kirby NA, and Poulos DA**. Cough Following Transection of Spinal Cord at C-6. *Arch Phys Med Rehabil* 45: 1-8, 1964.
140. **Silva AC, Neder JA, Chiurciu MV, Pasqualin DC, da Silva RC, Fernadez AC, Lauro FA, de Mello MT, and Tufik S**. Effect of aerobic training on ventilatory muscle endurance of spinal cord injured men. *Spinal Cord* 36: 240-245, 1998.
141. **Sinderby C, Weinberg J, Sullivan L, Lindstrom L, and Grassino A**. Electromyographical evidence for exercise-induced diaphragm fatigue in patients with chronic cervical cord injury or prior poliomyelitis infection. *Spinal Cord* 34: 594-601, 1996.
142. **Sipski ML, and Richards JS**. Spinal cord injury rehabilitation: state of the science. *Am J Phys Med Rehabil / Assoc Acad Physiatr* 85: 310-342, 2006.
143. **Sonetti DA, Wetter TJ, Pegelow DF, and Dempsey JA**. Effects of respiratory muscle training versus placebo on endurance exercise performance. *Respir Physiol* 127: 185-199, 2001.
144. **Spengler CM, and Boutellier U**. Breathless legs? Consider training your respiration. *News Physiol Sci* 15: 101-105, 2000.
145. **Spengler CM, Roos M, Laube SM, and Boutellier U**. Decreased exercice blood lactate concentrations after respiratory endurance training in humans. *Eur J Appl Physiol Occup Physiol* 79: 299-305, 1999.
146. **Spungen AM, Grimm DR, Schilero G, Lenner R, Oei E, Bauman WA, Almenoff PL, and Lesser M**. Relationship of respiratory symptoms with smoking status and pulmonary function in chronic spinal cord injury. *J Spinal Cord Med* 25: 23-27, 2002.
147. **St Croix CM, Morgan BJ, Wetter TJ, and Dempsey JA**. Fatiguing inspiratory muscle work causes reflex sympathetic activation in humans. *J Physiol* 529: 493-504, 2000.
148. **Strauss DJ, Devivo MJ, Paculdo DR, and Shavelle RM**. Trends in life expectancy after spinal cord injury. *Arch Phys Med Rehabil* 87: 1079-1085, 2006.
149. **Stüssi C, Spengler CM, Knöpfli-Lenzin C, Markov G, and Boutellier U**. Respiratory muscle endurance training in humans increases cycling endurance without affecting blood gas concentrations. *Eur J Appl Physiol* 84: 582-586, 2001.
150. **Tow AM, Graves DE, and Carter RE**. Vital capacity in tetraplegics twenty years and beyond. *Spinal Cord* 39: 139-144, 2001.
151. **Uijl SG, Houtman S, Folgering HT, and Hopman MT**. Training of respiratory muscles in individuals with tetraplegia. *Spinal Cord* 37: 575-579, 1999.
152. **van Asbeck FW, Post MW, and Pangalila RF**. An epidemiological description of spinal cord injuries in The Netherlands in 1994. *Spinal Cord* 38: 420-424, 2000.
153. **Van Houtte S, Vanlandewijck Y, and Gosselink R**. Respiratory muscle training in persons with spinal cord injury: A systematic review. *Respir Med* 100: 1886-1895, 2006.
154. **Volianitis S, McConnell AK, and Jones DA**. Assessment of maximum inspiratory pressure. Prior submaximal respiratory muscle activity ('warm-up') enhances maximum inspiratory activity and attenuates the learning effect of repeated measurement. *Respiration; Int Review Thoracic Dis* 68: 22-27, 2001.
155. **Volianitis S, McConnell AK, Koutedakis Y, McNaughton L, Backx K, and Jones DA**. Inspiratory muscle training improves rowing performance. *Med Sci Sports Exerc* 33: 803-809, 2001.
156. **Wells GD, Plyley M, Thomas S, Goodman L, and Duffin J**. Effects of concurrent inspiratory and expiratory muscle training on respiratory and exercise performance in competitive swimmers. *Eur J Appl Physiol* 94: 527-540, 2005.
157. **Wen AS, Woo MS, and Keens TG**. How many maneuvers are required to measure maximal inspiratory pressure accurately. *Chest* 111: 802-807, 1997.
158. **Williams JS, Wongsathikun J, Boon SM, and Acevedo EO**. Inspiratory muscle training fails to improve endurance capacity in athletes. *Med Sci Sports Exerc* 34: 1194-1198, 2002.
159. **Wilson TA, Rehder K, Krayer S, Hoffman EA, Whitney CG, and Rodarte JR**. Geometry and respiratory displacement of human ribs. *J Appl Physiol* 62: 1872-1877, 1987.
160. **Winslow C, and Rozovsky J**. Effect of spinal cord injury on the respiratory system. *Am J Phys Med Rehabil / Assoc Acad Physiatr* 82: 803-814, 2003.
161. **Yarkony GM, Roth EJ, Cybulski GR, and Jaeger RJ**. Neuromuscular stimulation in spinal cord injury. II: Prevention of secondary complications. *Arch Phys Med Rehabil* 73: 195-200, 1992.

162. **Zupan A, Savrin R, Erjavec T, Kralj A, Karcnik T, Skorjanc T, Benko H, and Obreza P**. Effects of respiratory muscle training and electrical stimulation of abdominal muscle on respiratorycapabilities in tetraplegic patients. *Spinal Cord* 35: 540-545, 1997.



Chapter 2

Determinants and Lesion-dependent Impairments of Respiratory Function in Spinal Cord Injury

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Submitted

Abstract

Objective: To assess the influences of personal and lesion characteristics on the impairments of lung function and respiratory muscle pressure in subjects with spinal cord injury (SCI), one year after discharge from inpatient rehabilitation.

Methods: This study was performed as cross-sectional, multi-centre study, including eight SCI rehabilitation centres. 129 subjects performed lung function measurements and 41 out of these performed additional respiratory muscle pressure measurements. Multivariate regression equations were calculated for four different groups, i.e. subjects with motor complete paraplegia, incomplete paraplegia, motor complete tetraplegia and incomplete tetraplegia.

Results: While forced vital capacity and forced expiratory volume in 1 s were between 74% and 94% of able bodied predicted, peak expiratory flow was only between 54% in complete tetraplegics and 75% in incomplete paraplegics. Maximal expiratory muscle pressure showed the highest limitations with values between 14% predicted in complete teraplegics and 45% in incomplete paraplegics. Lesion level and gender were related to most respiratory variables. Age and height were related to lung function parameters only. Body weight and smoking had no significant influence on any of the tested parameters.

Conclusions: Expiratory muscle pressure is the most severely affected parameter within all SCI individuals. Motor complete tetraplegics were the subjects with the lowest lung function and respiratory muscle pressure generation and may therefore be at higher risk for respiratory complications. Clinicians are encouraged to regularly screen lung function and respiratory muscle pressure generation as well as motivate patients for respiratory muscle training, particularly after inpatient rehabilitation.

Introduction

A spinal cord injury (SCI) causes lesion-dependent losses of respiratory muscle innervation, which can lead to impairments in respiratory muscle function (27). Due to paralysis of most expiratory muscles in subjects with tetraplegia and high paraplegia, the ability to cough and clear secretion is decreased. Because of this, various types of respiratory diseases such as dyspnoea, pneumonia, or respiratory failure occur (9). Causes of respiratory complications are often multi-factorial and seem to be associated with low respiratory function (33, 15). Therefore, detailed knowledge of lesion-dependent impairments and factors determining lung function and respiratory muscle pressure in subjects with SCI, two years after injury, should be evaluated as a basic indicator for preventative measures. Currently, only little knowledge exists about factors influencing respiratory function in SCI. Related studies are limited to the assessment of lung function in chronic SCI around 15 to 20 years post injury (5, 21). To our knowledge, only limited information is available on respiratory muscle pressure (24) and none on its associations to lung function in subjects with SCI. The present study aims to fill this gap with respect to subjects in the post-acute stage of SCI by investigating the following aspects:

1) To study lung function and respiratory muscle pressure in relation to lesion level and completeness in subjects with SCI, one year after discharge from inpatient rehabilitation.
2) To find determinants (i.e. level and completeness of the lesion, age, gender, height, weight and smoking) of lung function, in- and expiratory muscle pressure and inspiratory muscle endurance in subjects with SCI.
3) To find associations between lung function and respiratory muscle pressure parameters.

Methods

This study was part of the Dutch research program 'Physical strain, work capacity and mechanisms of restoration of mobility in the rehabilitation of persons with SCI' (12).

Subjects

Persons with SCI were recruited from eight SCI rehabilitation centres in the Netherlands, one year after discharge from inpatient rehabilitation. Inclusion criteria were a traumatic SCI, wheelchair dependency and an age range between 18 and 65 years. Prior to testing subjects were extensively screened by a physician and physical therapist. Potential participants were excluded if they had cardio-respiratory disorders (4), a resting diastolic blood pressure higher

than 90 mmHg, or a systolic blood pressure higher than 180 mmHg, and if they had one or more of the following diseases: COPD; severe atelectasis; lung emphysema with O_2-dependency, a history of pneumothorax, a progressive disease (e.g. ALS, MS), a psychiatric problem or no mastery of the Dutch language. Level and completeness of injury were determined by a physician according to the American Spinal Injury Association Scale (7). Finally, 129 subjects were included in the present study and completed the lung function measurements. Out of these 129 subjects, 41 subjects completed additional respiratory muscle pressure measurements.

Protocol

All participants completed an informed consent form after being informed about the testing procedure. The Medical Ethics Committee approved all tests and protocols. On the test day, participants were asked to consume a light meal only, to refrain from smoking, drinking coffee and alcohol at least two hours prior to testing and to void their bladder directly before testing. Eight trained paramedical research assistants who worked in the participating rehabilitation centres conducted the tests. All research assistants received extensive training in how to conduct the tests. The same equipment was used for each measurement, after standardized calibration, in the eight participating centres. Personal characteristics were derived from questionnaire data and body mass was measured immediately before the assessment of respiratory function.

Lung function measurements

Lung function parameters were measured using a cardio-respiratory measurement device (Oxycon Delta, Jaeger, Hoechberg, Germany) which was calibrated before each test. Lung function measurements were performed according to a standardized protocol (3) and consisted of forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), forced inspiratory volume in 1 s (FIV_1), peak expiratory flow (PEF) and peak inspiratory flow (PIF). Participants had to breathe through a mouthpiece while wearing a nose clip. Each measurement was repeated until three measurements were registered within ± 5% of each other. The highest value measured for each parameter was then used for further analysis. Age-gender- and height-corrected reference values (1) (100% predicted) for FVC, FEV_1 and PEF of able bodied subjects were used to compare our measured values.

Respiratory muscle pressure and incremental threshold loading tests

Peak inspiratory muscle pressure (Pi_{max}) and peak expiratory muscle pressure (Pe_{max}) were measured by an electronic manometer (Threshold meter (self made); Dept. of Physiology,

Radboud University, Nijmegen, The Netherlands) that fed into a personal computer for the recording of the data and which we connected to a mouthpiece with a small leak to prevent glottis closure. For measurements of maximal respiratory muscle pressure subjects were in an upright sitting position, wearing a nose clip and breathing through a mouthpiece. Pi_{max} was measured from residual volume and Pe_{max} was measured from total lung capacity. Subjects repeated each manoeuvre until three measurements were recorded within a range of ± 5%. Maximum pressures had to be maintained for at least 1 s. The highest plateau pressures (1 s) of Pi_{max} and Pe_{max} were used for analysis (32). Age- and gender-corrected reference values of able bodied subjects (8) were calculated for our groups of SCI subjects for Pi_{max} and Pe_{max} in order to compare the measured values to able bodied subjects 100% predicted. After a recovery period of 10 min, a subsequent test was performed to determine inspiratory threshold endurance time (t_{endu}) and load (P_{endu}). This test was conducted with an inspiratory threshold-loading device (Threshold IMT, Respironics, Herrsching, Germany). All participants started at an inspiratory load of 0.7 kPa, which had to be kept up for 1 min with a paced inspiration time of 3 s and expiration time of 4 s. Thereafter, the inspiratory load was instantly increased by 15% of the individual Pi_{max} and participants had to perform the test for a second minute. This procedure was repeated until participants were no longer able to sustain the actual load. When the maximal load of the device (4.1 kPa) was achieved, subjects had to sustain this load as long as possible with a maximum of 3 min. The duration of the whole test (t_{endu}) and the load at test break-off (P_{endu}) were used for further analysis.

Statistical analysis

Descriptive statistics (means ± SD) for group characteristics and respiratory function were calculated for each parameter and separately for subject groups with a motor complete tetraplegia, incomplete tetraplegia, complete paraplegia and incomplete paraplegia.

Differences in personal and lesion characteristics between the group that performed lung function measurements only (n = 88) and the group that performed additional respiratory muscle pressure testing (n = 41) were evaluated by unpaired t-tests using Systat (Systat Version 10.2; Systat Software Inc., San Jose, USA). Differences between lesion groups for able bodied subjects percentage predicted values of FVC, FEV_1, PEF, Pi_{max} and Pe_{max} were calculated using one-way ANOVA with Bonferroni post-hoc tests (Systat) to localize significant differences between groups. Significance was set to $p < 0.05$.

In order to determine the relationship between personal and lesion characteristics and lung function and respiratory muscle pressure, the multilevel modelling program MLwin (MLwin Version 1.1; Centre for Multilevel Modelling, Institute for Education; London, UK) (29) was used. Outcome variables were FVC, FEV_1, FIV_1, PEF, PIF, Pi_{max}, Pe_{max}, P_{endu} and t_{endu}. The hierarchy in the data was based on the individual participants (level 1) who were grouped in

the rehabilitation centres (level 2). As potential influencing factors on respiratory function, the level (subjects with paraplegia = 1, subjects with tetraplegia = 0) and completeness of the lesion (complete = 1, incomplete = 0), gender (male = 1, female = 0), age (years), height (m), weight (kg) as well as current smoking (current smoker = 1, non-smoker = 0) and former smoking (former smoker = 1, non-smoker = 0) were added one by one to a basic univariate multilevel regression model. Independent variables with p-values < 0.1 were included in a subsequent multilevel model, which was followed by a backward selection procedure excluding non-significant determinants ($p > 0.05$) in order to create the final multivariate model.

In addition, a multiple linear regression analysis was used to determine whether there were significant associations between lung function parameters and respiratory muscle pressure. In case of a significant association between these parameters the personal and lesion characteristics were checked one by one for their confounding effect. This was defined as a change in beta of the independent variable of more than 10%. Eventually, all confounders were added to the final model.

Results

Participants' characteristics of the lung function group and the respiratory muscle pressure group showed no significant differences (Table 1 and 2).

Table 1: Participants' characteristics of the whole group (lung function testing)

	gender [male / female]	**TPI** [months]	**age** [years]	**height** [m]	**weight** [kg]	**smoker** [%]
Subjects with complete tetraplegia	20 / 6	28.5 ± 5.2	29 ± 10	1.77 ± 0.09	76 ± 16	65
Subjects with incomplete tetraplegia	10 / 5	22.3 ± 6.2	48 ± 9	1.74 ± 0.07	73 ± 14	60
Subject with complete paraplegia	48 / 17	22.0 ± 5.1	39 ± 14	1.79 ± 0.09	78 ± 15	46
Subject with incomplete paraplegia	19 / 4	20.1 ± 3.3	42 ± 16	1.78 ± 0.10	79 ± 20	35
Whole group	**97 / 32**	**23.0 ± 5.7**	**38 ± 14**	**1.78 ± 0.09**	**77 ± 16**	**50**

TPI = time post injury

Table 2: Participants' characteristics of the group that performed additional respiratory muscle pressure measurements

	gender [male / female]	**TPI** [months]	**age** [years]	**height** [m]	**weight** [kg]	**smoker** [%]
Subjects with complete tetraplegia	6 / 2	28.5 ± 3.1	28 ± 11	1.78 ± 0.08	80 ± 20	38
Subjects with incomplete tetraplegia	5 / 1	22.7 ± 7.1	49 ± 6	1.76 ± 0.04	77 ± 19	83
Subject with complete paraplegia	13 / 5	23.1 ± 4.2	36 ± 13	1.80 ± 0.08	79 ± 12	50
Subject with incomplete paraplegia	8 / 1	21.7 ± 3.7	45 ± 15	1.77 ± 0.12	80 ± 28	44
Whole group	32 / 9	23.8 ± 4.9	39 ± 14	1.79 ± 0.09	79 ± 18	51

TPI = time post injury

Lung function

The means ± SD of the lung function parameters of the measured SCI group as a whole were 4.09 ± 1.29 l FVC (87 ± 22% pred.), 3.32 ± 1.04 l FEV_1 (86 ± 22% pred.), 3.62 ± 1.19 l FIV_1, 5.94 ± 1.88 l/s PEF (67 ± 20% pred.) and 4.97 ± 1.7 1/s PIF. Motor complete subjects generally showed lower values than motor incomplete subjects and subjects with tetraplegia showed lower values than subjects with paraplegia (Table 3, Figure 1).

Table 3: Mean ± SD [%] of gender, age and height corrected lung function as well as gender and age corrected respiratory muscle pressure of able bodied 100% predicted

	FVC %	FEV_1 %	PEF %	Pi_{max} %	Pe_{max} %
Subjects with complete tetraplegia	74 ± 21	76 ± 22	54 ± 17	56 ± 17	14 ± 7
Subjects with incomplete tetraplegia	94 ± 26*	90 ± 26	73 ± 23*	53 ± 23	25 ± 8
Subject with complete paraplegia	89 ± 20*	87 ± 20	69 ± 18*	82 ± 24	36 ± 17*
Subject with incomplete paraplegia	94 ± 20*	92 ± 24	75 ± 20*	56 ± 25	45 ± 12*

FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; PEF = peak expiratory flow; Pi_{max} = maximal inspiratory muscle pressure; Pe_{max} = maximal expiratory muscle pressure; * = significant difference to subjects with complete teraplegia

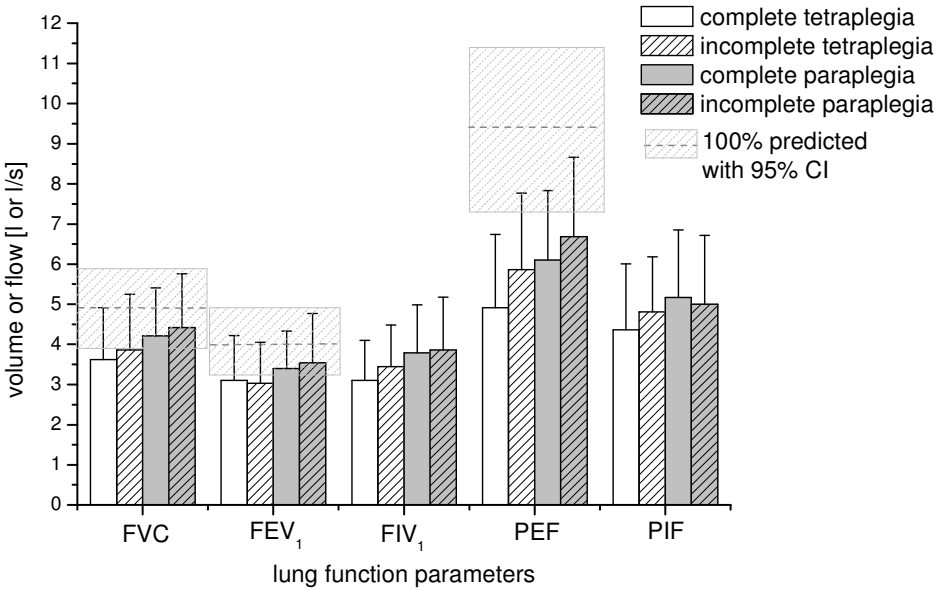

Figure 1: Measured mean values and standard deviations for forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), forced inspiratory volume in 1 s (FIV_1), peak expiratory flow (PEF) and peak inspiratory flow (PIF) given for the four lesion-related subgroups. Gender-, age- and height-corrected able bodied subjects 100% predicted with 95% confidence intervals (CI) are given for FVC, FEV_1 and PEF.

All lung function parameters were significantly associated to the level of injury. Men showed significantly higher values than women (except for PEF), younger subjects showed higher values than older ones and taller subjects showed higher values than smaller ones (except for PIF). Smoking and body weight had no significant influence on any of the tested lung function parameters (Table 4). Using the regression equations presented in Table 4, allows calculating the predicted lung function and respiratory muscle pressure values for any subject with SCI that meet the inclusion criteria of this study. The calculation of the predicted FVC of e.g. a male subject with motor complete paraplegia, 37 years old, 1.78 m tall and 72 kg body weight would be as follows:

FVC = -4.60 *(constant)* + 0.49 *(paraplegia)* + 0.83 *(male)* - (37 x 0.02) *(age)* + (1.78 x 4.80) *(height)* = 4.524 l

Table 4: Regression coefficients (βi) for lung function and respiratory muscle pressure parameters from the multivariate multilevel regression analysis

	subjects	**β_0**	**β_1**	**β_2**	**β_3**	**β_4**	**β_5**
	[n]	(constant)	(level)	(compl.)	(gender)	(age)	(height)
FVC (l)	[128]	-4.60	0.49*	n.s.	0.83***	-	4.80***
FEV_1 (l)	[128]	-3.10	0.34*	n.s.	0.55**	-	3.75***
FIV_1 (l)	[128]	-2.98	0.53**	n.s.	0.71**	-	3.60***
PEF (l/s)	[128]	-7.24	1.00**	-1.09***	n.s.	-0.025*	8.02***
PIF (l/s)	[127]	4.56	0.66*	n.s.	1.23***	-0.03**	n.s.
Pe_{max} (kPa)	[41]	3.59	4.19***	-2.13*	2.01*	n.s.	n.s.
Pi_{max} (kPa)	[39]	2.92	1.88*	2.04*	2.68**	n.s.	n.s.
P_{endu} (kPa)	[38]	2.09	0.75*	n.s.	0.91**	n.s.	n.s.
t_{endu} (kPa)	[38]	3.08	1.36**	n.s.	n.s.	n.s.	n.s.

FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; FIV_1 = forced inspiratory volume in 1 s; PEF = peak expiratory flow; PIF = peak inspiratory flow; Pi_{max} = maximal inspiratory muscle pressure; Pe_{max} = maximal expiratory muscle pressure; P_{endu} = maximal pressure of inspiratory threshold endurance test; t_{endu} = time of inspiratory threshold endurance test; β = regression coefficient for each independent variable; level: 1 = subject with paraplegia, 0 = subjects with tetraplegia; completeness: 1 = complete, 0 = incomplete; gender: 1 = male, 0 = female; age = years; height = m; * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$; n.s. = not significant. Note that body weight and smoking had no significant influence on any of the tested parameters and are therefore not shown in Table 4.

Maximal respiratory muscle pressure test and incremental threshold loading test

Mean Pi_{max} of the whole group was at 7.54 ± 3.02 kPa (67 ± 25% pred.). Mean Pe_{max} of the whole group reached only 6.56 ± 3.58 kPa (32 ± 17% pred.). Respiratory muscle pressure of lesion-dependent subgroups was clearly below able bodied subjects 100% predicted after correction for gender and age (8) (Table 4, Figure 2). Pi_{max} and Pe_{max} were significantly associated with the level and completeness of the lesion as well as with gender (Table 4). Subjects with paraplegia showed higher values than subjects with tetraplegia and men showed higher values than women. Age, height, body weight and smoking had no significant influence on any of the tested respiratory muscle pressure parameters. P_{endu} was associated with lesion level and gender while t_{endu} was influenced by lesion level only (Table 4).

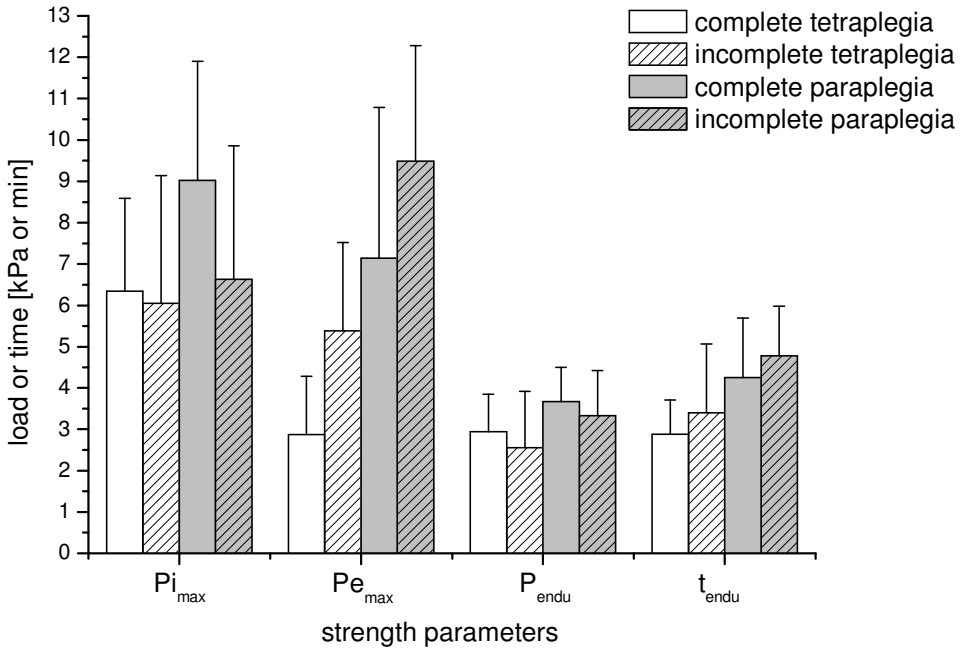

Figure 2: Measured mean values and standard deviations for maximal inspiratory pressure (Pi_{max}), maximal expiratory pressure (Pe_{max}), maximal load (P_{endu}) and time (t_{endu}) of the incremental threshold-loading test given for the four lesion-related subgroups.

Associations between respiratory muscle pressure and lung function

Pe_{max} and Pi_{max} were significant determinants of most lung function parameters (Table 5). Gender was a confounder for all significant associations and sometimes level and completeness of the lesion or age had an additional confounding effect (Table 5).

Table 5: Significant associations between lung function and respiratory muscle pressure parameters, as well as significant confounders in the multi-variate multilevel regression model

	constant	**pressure parameter**		**confounding variables**		
	β_0	β_1	β_2 (level)	β_3 (compl.)	β_3 (gender)	β_4 (age)
FVC (l)	1.93	0.17*** Pe_{max}	-0.23	0.40	1.09**	-
	1.90	0.24*** Pi_{max}	-	-0.49*	0.65*	-
	1.34	0.55*** P_{endu}	-	-	1.07***	-
	2.10	0.24* t_{endu}	-		1.10**	-
FEV_1 (l)	1.63	0.12*** Pe_{max}	-0.30	0.41	0.92**	-
	1.93	0.17*** Pi_{max}	-	-	0.57*	-0.013
	1.21	0.37** P_{endu}	-	-	0.94**	-
FIV_1 (l)	1.89	0.09 Pe_{max}	-0.12	0.46	1.08**	-
	1.45	0.20*** Pi_{max}	-	-	0.63*	-
	0.97	0.58*** P_{endu}	-	-	0.81*	-
PEF (l/s)	4.71	0.12 Pe_{max}	-	-	1.26*	0.019
	3.39	0.29** Pi_{max}	-	-0.70	0.73	-
PIF (l/s)	2.47	0.28*** Pi_{max}	-0.66	-	0.86	-
	2.11	0.65* P_{endu}	-0.44	-	1.21	-

FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; FIV_1 = forced inspiratory volume in 1 s; PEF = peak expiratory flow; PIF = peak inspiratory flow; Pi_{max} = maximal inspiratory muscle pressure; Pe_{max} = maximal expiratory muscle pressure; P_{endu} = maximal pressure of inspiratory threshold endurance test; t_{endu} = time of inspiratory threshold endurance test; β = regression coefficient for each independent variable; level: 1 = subject with paraplegia, 0 = subjects with tetraplegia; completeness: 1 = complete, 0 = incomplete; gender: 1 = male, 0 = female; age = years; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; - = no confounder; Note that only respiratory muscle pressure parameters with significant associations to lung function parameters are listed and height, body weight and smoking were no confounders to any of the tested parameters and are therefore not shown in Table 5.

Discussion

Lung function and respiratory muscle pressure in subjects with different levels of SCI are influenced by similar parameters as able bodied subjects (3, 8), i.e. gender, age and height - but additionally by the lesion level and in some cases also by completeness of the lesion (PEF, Pe_{max} and Pi_{max}). Motor complete tetraplegics are the most severely affected subjects,

with significantly lower FVC and PEF than all other SCI groups, and significantly lower Pe_{max} than subjects with paraplegia.

Lung function

Compared to able bodied subjects' predicted values, FVC and FEV_1 were rather normal in subjects with paraplegia, but reduced by around 25% in complete tetraplegics. Regression coefficients of age represent a decrease in lung function of 0.2 to 0.3 l per 10 years of age. These coefficients for subjects with SCI, one year after discharge from inpatient rehabilitation, are in accordance with those for able bodied subjects (1). Cross-sectional studies (5, 22) of subjects with chronic SCI, 19 and 16 years post injury, showed lower FVC and FEV_1 values than those found in our subjects (22). Age and time post injury or the combination of both seems to be important factors decreasing respiratory function over time. In addition, a decrease in lung function may be possible because of rib cage stiffening, particularly in subjects with tetraplegia (13). Nevertheless, neither from our data nor from other cross-sectional studies (5, 22) of subjects with chronic SCI a potential decrease in lung volumes per year post injury can be extrapolated. Longitudinal studies beyond the first two years post injury and over at least 10 years post injury, including large groups of subjects are needed to evaluate this interesting aspect.

To produce an effective cough a PEF of at least 5-6 l/s is necessary (16). Results of the present study show that the median PEF of subjects with tetraplegia was around 5-6 l/s. This indicates that about 50% of this group is not able to produce an effective cough and may therefore be at high risk for respiratory tract infections. PEF appears to be a relevant parameter for clinical practice. It could be a useful screening parameter in subjects with SCI in order to detect a potential risk for respiratory complications at an early stage (i.e. PEF below 5 l/s).

Recently, it has been shown that FVC, which also depends on a deep inspiration, correlates with voluntary cough capacity in subjects with tetraplegia (19). Even if expiration is the weakest part of respiration in SCI, the importance of the inspiratory lung function should not be underestimated. A fast and deep inspiration leads to an advantageous position of the diaphragm and a higher lung elastic recoil that can help to increase the power of expiration (6, 30). This may be an important aspect to improve cough capacity, particularly in subjects with tetraplegia, where most of the expiratory muscles are paralyzed and who can not produce a PEF over 5-6 l/s (33).

The finding that smoking did not influence any of the tested parameters was surprising. Since 50% of the subjects included in this study were active or former smokers, our finding could not be a problem of power. Other studies found significant negative influences of smoking on lung function in subjects with SCI (5, 23). Influences of smoking on lung function were also assessed dichotomously in these studies (5, 23). These subjects were older (mean age of 45 to 50 yrs) and had a longer duration of injury (16 and 19 years) than subjects in the present study. This shows that smoking may have negative consequences particularly in the chronic stage of SCI. Thus, smoking cessation should be encouraged as early as possible after SCI.

Maximal respiratory muscle pressure

Mean Pi_{max} and Pe_{max} were even more below the able bodied subjects' reference values than the values of lung function in all four SCI groups (Table 3). Pe_{max} of all of our groups was below 50% of the able bodied subjects predicted. This indicates that Pe_{max} in subjects with SCI is strongly affected by the lesion-dependent absence of expiratory muscle innervation. The degree to which Pi_{max} is reduced in all lesion level groups shows that it is the respiratory muscle pressure rather than the lung function that is more affected in subjects with SCI (Table 3). As indicated by our data, training of the remaining expiratory (14, 18) as well as inspiratory (18, 20) muscles in order to improve the cough effectiveness and to decrease other respiratory complications seems to be beneficial (11, 25, 31).

Associations between respiratory muscle pressure and lung function

We found that an increase of 1 kPa in Pi_{max} is associated with a higher increase in lung function than the same increase in Pe_{max} (Table 5). Resistive inspiratory muscle training performed by subjects with chronic tetraplegia showed that respiratory muscle pressure training over the duration of eight weeks, administered 15 min and twice daily, improved Pi_{max} by 2 kPa and Pe_{max} by 1.5 kPa (31). According to our regression equations (Table 5) such an increase in Pi_{max} would be associated with an improvement in FVC of 0.48 l or 0.58 l/s in PEF. Related to our predicted loss in FVC of 0.2-0.3 l per 10 years of age, this increase which may be achieved by training seems to justify respiratory muscle training in individuals with SCI. Particularly for subjects with tetraplegia, who often show FVC between 1 and 2 l, such an increase may improve respiration substantially. Improvements in respiratory muscle pressure may therefore be of high importance when the PEF lies around or below the critical value for active coughing of 5-6 l/s.

Study limitations

As a result of the inclusion criteria 'wheelchair-dependent' for the whole Dutch research programm (11), the majority of the participants had a motor complete lesion. Therefore, the strength of the calculated models may be higher for subjects with a motor complete lesion than for those with incomplete lesions. Because of the higher percentage of men, our models may be less accurate for women. Nevertheless, our study represents a normal gender distribution within the SCI population (2, 10, 26).

Conclusion

PEF and Pe_{max} were the most severely affected parameters, especially in subjects with motor complete tetraplegia. About 50% of the subjects with motor complete tetraplegia were below the critical level of 5-6l/s PEF that is necessary to produce an effective cough and may therefore be exposed to an increased risk for respiratory complications. Thus, subjects with motor complete tetraplegia should be screened regularly for the prevention of respiratory complications including PEF and Pe_{max} measurements. Further, clinicians are encouraged to motivate and brief patients for respiratory muscle training especially after inpatient rehabilitation.

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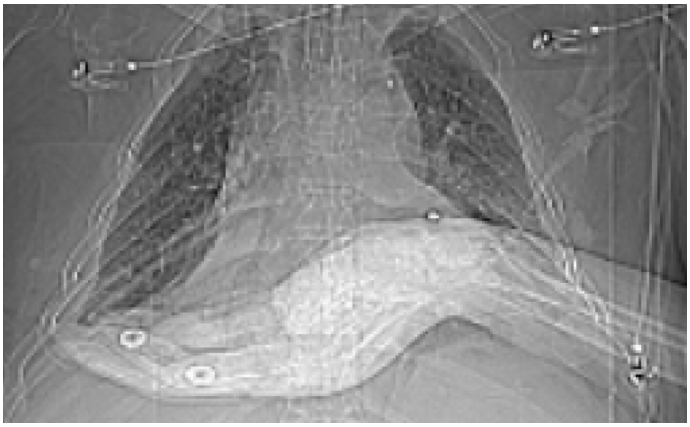
References

1. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis* 144: 1202-1218, 1991.
2. Spinal cord injury. Facts and figures at a glance. *J Spinal Cord Med* 28: 379-380, 2005.
3. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 152: 1107-1136, 1995.

4. **ACSM**. *ACSM's guidelines for exercise testing and prescription*. Baltimore: American College of Sports Medicine, 2000, p. 368.
5. **Almenoff PL, Spungen AM, Lesser M, and Baumann WA**. Pulmonary function survey in spinal cord injury: influences of smoking and level and completeness of injury. *Lung* 173: 297-306, 1995.
6. **Altarifi A, Badr MS, and Tzelepis GE**. Maximal dynamic expiratory pressures with fast and slow inspirations. *Eur J Appl Physiol* 89: 74-78, 2003.
7. **ASIA**. *International Standards for Neurological Classification of SCI*. Chicago: American Spinal Injury Association, 2000.
8. **Black LF, and Hyatt RE**. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 99: 696-702, 1969.
9. **Brown R, DiMarco AF, Hoit JD, and Garshick E**. Respiratory dysfunction and management in spinal cord injury. *Respir Care* 51: 853-868;discussion 869-870, 2006.
10. **Celani MG, Spizzichino L, Ricci S, Zampolini M, and Franceschini M**. Spinal cord injury in Italy: A multicenter retrospective study. *Arch Phys Med Rehabil* 82: 589-596, 2001.
11. **Cheng PT, Chen CL, Wang CM, and Chung CY**. Effect of neuromuscular electrical stimulation on cough capacity and pulmonary function in patients with acute cervical cord injury. *J Rehabil Med* 38: 32-36, 2006.
12. **de Groot S, Dallmeijer AJ, Post MW, van Asbeck FW, Nene AV, Angenot EL, and van der Woude LH**. Demographics of the Dutch multicenter prospective cohort study 'Restoration of mobility in spinal cord injury rehabilitation'. *Spinal Cord* 44: 668-675, 2006.
13. **Estenne M, Gevenois PA, Kinnear W, Soudon P, Heilporn A, and De Troyer A**. Lung volume restriction in patients with chronic respiratory muscle weakness: the role of microatelectasis. *Thorax* 48: 698-701, 1993.
14. **Estenne M, Knoop C, Vanvaerenbergh J, Heilporn A, and De Troyer A**. The effect of pectoralis muscle training in tetraplegic subjects. *Am Rev Respir Dis* 139: 1218-1222, 1989.
15. **Fishburn MJ, Marino RJ, and Ditunno JF, Jr.** Atelectasis and pneumonia in acute spinal cord injury. *Arch Phys Med Rehabil* 71: 197-200, 1990.
16. **Fugl-Meyer AR**. The respiratory system. In: *Handbook of clinical Neurology*, edited by Vinken PJ, and Bruyn GW. New York: American Elsevier, 1976, p. 335-349.
17. **Jain NB, Brown R, Tun CG, Gagnon D, and Garshick E**. Determinants of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC in chronic spinal cord injury. *Arch Phys Med Rehabil* 87: 1327-1333, 2006.
18. **Kang SW, Kang YS, Sohn HS, Park JH, and Moon JH**. Respiratory muscle pressure and cough capacity in patients with duchenne muscular dystrophy. *Yonsei Med J* 47: 184-190, 2006.
19. **Kang SW, Shin JC, Park CI, Moon JH, Rha DW, and Cho DH**. Relationship between inspiratory muscle pressure and cough capacity in cervical spinal cord injured patients. *Spinal Cord* 44: 242-248, 2006.
20. **Liaw MY, Lin MC, Cheng PT, Wong MK, and Tang FT**. Resistive inspiratory muscle training: its effectiveness in patients with acute complete cervical cord injury. *Arch Phys Med Rehabil* 81: 752-756, 2000.
21. **Linn WS, Adkins RH, Gong H, Jr., and Waters RL**. Pulmonary function in chronic spinal cord injury: a cross-sectional survey of 222 southern California adult outpatients. *Arch Phys Med Rehabil* 81: 757-763, 2000.
22. **Linn WS, Spungen AM, Gong H, Adkins RH, Baumann WA, and Waters RL**. Forced vital capacity in two large outpatient populations with chronic spinal cord injury. *Spinal Cord* 39: 263-268, 2001.
23. **Linn WS, Spungen AM, Gong H, Jr., Bauman WA, Adkins RH, and Waters RL**. Smoking and obstructive lung dysfunction in persons with chronic spinal cord injury. *Arch Phys Med Rehabil* 26: 28-35, 2003.
24. Mateus SR, Beraldo PS, Horan TA. Maximal static mouth respiratory pressure in spinal cord injured patients: correlation with motor level. *Spinal Cord* 45:569-75, 2007.
25. **Rutchik A, Weissman AR, Almenoff PL, Spungen AM, Bauman WA, and Grimm DR**. Resistive inspiratory muscle training in subjects with chronic cervical spinal cord injury. *Arch Phys Med Rehabil* 79: 293-297, 1998.
26. **Schonherr MC, Groothoff JW, Mulder GA, and Eisma WH**. Rehabilitation of patients with spinal cord le sions in The Netherlands: an epidemiological study. *Spinal Cord* 34: 679-683, 1996.

27. **Sipski ML, and Richards JS**. Spinal cord injury rehabilitation: state of the science. *Am J Phys Med Rehabil / Assoc Acad Physiatr* 85: 310-342, 2006.
28. **Strauss DJ, Devivo MJ, Paculdo DR, and Shavelle RM**. Trends in life expectancy after spinal cord injury. *Arch Phys Med Rehabil* 87: 1079-1085, 2006.
29. **Twisk JW**. *Applied Longitudinal Data Analysis for Epidemiology, A Practical Guide*. Amsterdam: Cambridge University Press, 2003.
30. **Tzelepis GE, Zakynthinos S, Vassilakopoulos T, Geroulanos S, and Roussos C**. Inspiratory maneuver effects on peak expiratory flow. Role of lung elastic recoil and expiratory pressure. *Am J Respir Crit Care Med* 156: 1399-1404, 1997.
31. **Wang TG, Wang YH, Tang FT, Lin KH, and Lien IN**. Resistive inspiratory muscle training in sleep-disordered breathing of traumatic tetraplegia. *Arch Phys Med Rehabil* 83: 491-496, 2002.
32. **Windisch W, Hennings E, Sorichter S, Hamm H, and Criee CP**. Peak or plateau maximal inspiratory mouth pressure: which is best? *Eur Respir J* 23: 708-713, 2004.
33. **Winslow C, and Rozovsky J**. Effect of spinal cord injury on the respiratory system. *Am J Phys Med Rehabil / Assoc Acad Physiatr* 82: 803-814, 2003.



Chapter 3

Time-Courses of Lung Function and Respiratory Muscle Pressure Generating Capacity after Spinal Cord Injury: A Prospective Cohort Study

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Abstract

Objective: To investigate the time-courses of lung function and respiratory muscle pressure generating capacity after spinal cord injury.

Methods: 109 subjects with recent, motor complete spinal cord injury were assessed in a multi-centre, prospective cohort study. Lung function and respiratory muscle pressure generating capacity were measured at first mobilization, at discharge from inpatient rehabilitation and one year after discharge. Lung function was measured in all 109 subjects and 55 out of these performed additional measurements of respiratory muscle pressure generating capacity. Trajectories of respiratory muscle function for different lesion level groups were assessed by multivariate multilevel regression models.

Results: Forced vital capacity, forced expiratory volume in 1 s and maximal inspiratory muscle pressure generating capacity significantly increased during and after inpatient rehabilitation. Forced inspiratory volume in 1 s, peak inspiratory flow, peak expiratory flow and maximal expiratory muscle pressure generating capacity only increased during inpatient rehabilitation but not thereafter. Increasing lesion level had a negative effect on all measured lung function parameters, as well as on maximal in- and expiratory muscle pressure generating capacity.

Conclusion: Respiratory function improved during inpatient rehabilitation, but only forced vital capacity, forced expiratory volume in 1 s and maximal inspiratory muscle pressure generating capacity further improved thereafter. Especially expiratory muscle function and subjects with tetraplegia should be screened and trained regularly.

Introduction

Pulmonary complications occur in 50-67% of persons with a spinal cord injury (SCI) (17, 25), with pneumonia being the most common cause of death in individuals with tetraplegia (15). A recent prospective mortality study showed that the respiratory system was responsible for the cause of death in 28% of the cases during the first year after injury and in 22% thereafter (21). In cross-sectional studies it has been shown that with increasing lesion level lung function decreases (52) and respiratory tract infections increase (17).

In individuals with SCI, the pulmonary system is often affected due to lesion-dependent losses of respiratory muscle innervations (2, 3, 31, 38). While persons with paraplegia lack proper innervation of the abdominal muscles and, depending on the lesion level, (parts of) the intercostal muscles, persons with tetraplegia lack most of the expiratory and even some of the auxiliary inspiratory muscles (14). The loss of respiratory muscle innervations mainly decreases cough capacity and therefore secretion clearance is reduced especially in subjects with high tetraplegia (43). Thus, respiratory muscle pressure generating capacity may be in direct relation with respiratory tract infections; however studies to prove this assumption are missing.

Although Fugl-Meyer et al. (18, 20) assessed respiratory function in subjects with SCI as soon as the early seventies, still little is known about longitudinal changes of respiratory function in SCI. Sinderby et al. (45) studied diaphragmatic function in subjects with tetraplegia early (1-3 years) and 10 or more years post injury. They found no significant changes in vital capacity and transdiaphragmatic pressure from early to more than 10 years post injury. Some small studies that evaluated trajectories of lung function early after SCI found strong improvements during the first 6 months after injury with smaller improvements thereafter (4, 7, 22, 34). Possibly the impact of spinal shock, which usually disappears within the first 4-6 months after injury, stabilizes pulmonary function and may therefore be responsible for this finding (35). All longitudinal studies show data which is either exclusively including subjects with tetraplegia (4, 5, 22, 34) or which is merely assessing a low number of subjects (5, 7, 34).

As described above, lung function and respiratory muscle pressure generating capacity seem to change over time and depend on the level of the lesion (18, 20, 33, 45). Nevertheless, the influence of lesion level and time on lung function and respiratory muscle pressure generating capacity is not yet approached through a longitudinal perspective.

A better understanding of lesion-dependence and trajectories of lung function and respiratory muscle impairments in persons with recent SCI would allow a better adjustment of therapeutic interventions which prevent complications and might further decrease mortality rates caused by respiratory tract infections.

Therefore, the purpose of this study was to describe trajectories of lung function and respiratory muscle pressure generating capacity in a large group of subjects with recent SCI

during and one year after inpatient rehabilitation, with respect to lesion level and personal factors. Gender, age, height, body weight and smoking were evaluated as personal factors, as they may influence respiratory function in addition to lesion characteristics and time.

Methods

This study was part of the Dutch research program 'Physical strain, work capacity and mechanisms of restoration of mobility in the rehabilitation of persons with SCI' (13).

Subjects

Persons with recent SCI from eight SCI rehabilitation centers in the Netherlands participated on a voluntary basis in this study between August 2000 and July 2003. Subjects were measured at the start of active rehabilitation (t_1), at the end of their inpatient rehabilitation (t_2) and one year after discharge (t_3).

Inclusion criteria for the current study were: an acute, motor complete SCI (ASIA A or B) and aged between 18 and 65 years. Potential participants were excluded if they had one or more of the following diseases: instable COPD, severe atelectasis, lung emphysema with O_2 dependency or a history of pneumothorax. Subjects were also excluded if they had a progressive disease, psychiatric problem or did not have enough knowledge of the Dutch language to understand the purpose of the study and the testing methods. Finally, 109 subjects were included in the present study and performed lung function measurement. Out of these 109, 55 subjects completed additional measurements of respiratory muscle pressure generating capacity. For investigating the time-courses of lung function and respiratory muscle pressure generating capacity, only data of those subjects who could perform the tests more than once were included in the analysis (i.e. 109 subjects for lung function and 55 subjects for respiratory muscle pressure generating capacity).

Participants' characteristics of the lung function group and the respiratory muscle pressure generating capacity subgroup are presented in Table 1 separately for the different lesion groups. There were no significant differences in personal characteristics between those subjects who performed only lung function measurements (n = 54) and those who performed respiratory muscle pressure generating capacity and lung function measurements (n = 55), (all p-values between 0.919 and 0.166).

Table 1: Participants' characteristics of the whole group [n = 109]; (lung function testing) and of the subgroup [n = 55] (testing of respiratory muscle pressure generating capacity)

	gender [men / women]	**age** [years]	**height** [m]	**weight** [kg]	**BMI** [kg/m^2]	**smoker before injury**	**current smoker**
Lung function measurements							
HT	14/6	36 ± 14	1.75 ± 0.08	71 ± 16	23.3 ± 5.2	30%	5%
LT	15/4	33 ± 10	1.79 ± 0.11	69 ± 11	21.6 ± 3.3	79%	26%
HP	23/7	43 ± 16	1.79 ± 0.09	77 ± 13	24.0 ± 3.1	33%	17%
LP	29/11	38 ± 13	1.78 ± 0.09	70 ± 12	21.9 ± 3.5	40%	30%
all subjects with SCI	81/28	38 ± 14	1.78 ± 0.09	72 ± 13	22.6 ± 3.8	47%	23%
Measurements of respiratory muscle pressure generating capacity							
subjects with tetraplegia	20/6	33 ± 11	1.79 ± 0.10	70 ± 15	22.0 ± 4.4	54%	15%
subjects with paraplegia	21/8	39 ±14	1.77 ± 0.09	72 ± 12	22.8 ± 3.3	48%	38%
all subjects with SCI	41/14	36 ± 13	1.78 ± 0.09	71 ± 13	22.4 ± 3.8	51%	27%

HT = subjects with high tetraplegia (C3-C5), LT = subjects with low tetraplegia (C6-C8), HP = subjects with high paraplegia (T1-T6), LP = subjects with low paraplegia (T7-T12), BMI = body mass index; SCI = spinal cord injury

Protocol

All subjects completed an informed consent form after they received information about the testing procedure. The medical ethics committee approved this study. On the test day, subjects were asked to consume a light meal only, to refrain from smoking, drinking coffee and alcohol at least 2 h prior to testing and to void their bladder directly before testing.

Lung function measurements

Lung function measurements were conducted using a cardio-pulmonary and respiratory testing device (Oxycon Delta, Jaeger, Hoechberg, Germany) which was calibrated before each test. Lung function measurements were performed according to a standardized protocol (1).

The following parameters were measured: forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), forced inspiratory volume in 1 s (FIV_1), peak expiratory flow (PEF) and peak inspiratory flow (PIF). Subjects had to breathe through a mouthpiece while wearing a nose clip. Each measurement was performed until 3 reproducible measurements within at least ± 5 % were registered. The highest measured value of each parameter was used for further analysis. In order to compare values of the present study and to get more insight on the respiratory impairment of subjects with para-and tetraplegia, we calculated gender-, height- and age-corrected 100 % predicted values for able bodied subjects using the regression equations of Quanier et al. (40).

Measurements of respiratory muscle pressure generating capacity

Maximal inspiratory and expiratory muscle pressure generating capacity (Pi_{max}, Pe_{max}) measured at the mouth, were performed with a calibrated, respiratory threshold meter (Instrumental Department, Radboud University Nijmegen, the Netherlands) connected to a personal computer. Pi_{max} and Pe_{max} were measured from residual volume and total lung capacity, respectively. Subjects had to breathe through a mouthpiece with a clip on their nose. To prevent measurement of muscle force of the cheeks, subjects had to sit with their elbows on a table and their hands on the cheeks. A small air leak in the mouthpiece prevented glottis closure. The highest pressure that could be maintained for 1 s was determined by the computer program. Each measurement was performed until 3 reproducible measurements within at least ± 5 % were registered. A rest period of at least 1 min between each effort was kept. The best values for Pi_{max} and Pe_{max} were used for analysis. Measurement of maximal inspiratory and expiratory pressures (Pi_{max} and Pe_{max}) at the mouth are widely used and accepted as measures of respiratory muscle pressure generating capacity (30, 37, 46). However, in subjects with SCI changes in abdominal compliance e.g. due to spasticity, may influence respiratory muscle pressure generating capacity (42).

After a resting period of 10 min, a further test was performed in order to determine inspiratory threshold muscle endurance time and pressure. This test was conducted with an inspiratory threshold meter (Threshold IMT, Respironics, Herrsching, Germany). All subjects started at an inspiratory pressure of 0.7 kPa. This pressure had to be kept up for 1 min with a paced inspiration time of 3 s and an expiration time of 4 s. When subjects were able to complete 1 min, inspiratory pressure was immediately increased by 15 % of the individual Pi_{max} and subjects completed the second min. This procedure was continued until subjects were no longer able to sustain the actual pressure, i.e. when target pressure could no longer be reached throughout the inspiration. If the maximal pressure of the device (4.1 kPa) was achieved, they had to sustain this pressure as long as possible with a maximum of 3 min. Time of the whole test (t_{endu}) and pressure at test break-off (P_{endu}) were used for further analysis.

Statistical analysis

Descriptive statistics (means ± standard deviations) for group characteristics were calculated for each parameter. Characteristics of the subjects who performed lung function measurements only (n = 54) and the respiratory muscle pressure generating capacity sub-group (n = 55) were compared using unpaired t-tests. Significance was set at $p < 0.05$. T-tests were performed with SPSS (Version 13.0; SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606, USA).

For analysis of the longitudinal data, a multilevel modelling program (Centre for Multilevel Modelling, Institute of Education, 20 Bedford Way, London WC1H 0AL, UK) (41, 47) was used. Multilevel regression analysis is suitable for longitudinal datasets since i) it allows dependency of repeated measures within the same person, ii) it accounts for the hierarchy of the longitudinal data used in our study where the repeated measurements (level 1) are nested within the subjects (level 2) which are nested within rehabilitation centres (level 3), and iii) the number of observations per person may vary (47). Outcome variables were FVC, FEV_1, FIV_1, PEF, PIF, Pi_{max}, Pe_{max}, P_{endu} and t_{endu}. Multilevel analysis was used to assess 1) the time-courses of lung function and respiratory muscle pressure generating capacity outcome measures during and 1-year after inpatient rehabilitation. Time was modeled using 2 dichotomous dummy variables with t_2 as reference, in order to calculate the change during ($\Delta t_1 t_2$) and after ($\Delta t_2 t_3$) inpatient rehabilitation; 2) to assess differences in trajectories for lung function data among subjects with different lesion levels. Therefore, four groups were defined: HT = subjects with high tetraplegia (C3-C5), LT = subjects with low tetraplegia (C6-C8), HP = subjects with high paraplegia (T1-T6) and LP = subjects with low paraplegia (T7-T12). To calculate differences among groups, 3 dummies were used and LT was determined as reference group. To assess trajectories of respiratory muscle pressure generating capacity, only two groups (paraplegic and tetraplegic) were built in order to not lose statistical power since only 55 subjects performed these measurements.

In a next step interactions between time- and group-dummies were added to the above described basic model. Interaction terms were only added to the final model if at least one of them was significant ($p < 0.05$).

To investigate a possible influence of personal factors, as known from able bodied subjects reference equations (6, 40), these factors were added one by one to the model: gender (male = 1, female = 0), age (years), height (m), weight (kg), former smoker, i.e. before injury (0 = non-smoker; 1 = former smoker) and current smoker (0 = non-smoker; 1 = current smoker) and evaluated whether they showed a significant ($p < 0.10$) influence on the outcome variables. After adding all significant ($p < 0.10$) personal factors to the basic model of time and group-dummies, a backward elimination technique was used until only determinants remained with a p-value < 0.05. Based on the final model, estimates for lung function and

respiratory muscle pressure generating capacity were calculated for the 4 lesion groups (lung function) and for subjects with para- and tetraplegia (respiratory muscle pressure generating capacity), respectively.

Results

There was no heterogeneity across the eight centres in any of the tested respiratory function parameters, i.e. that one centre systematically found higher or lower values for one parameter. Specific estimates for trajectories of these parameters were calculated for men only, and with subjects mean age (38 years) and height (1.78 m) (Figure 1 and 2). Presented models can be used to calculate estimated values for subject X at a certain time point after injury. For example, calculation of predicted FVC for a male subject with high tetraplegia, 38 years old and 1.78m tall, one year after inpatient rehabilitation would be as follows:

FVC = β of constant + β of Δt2-t3 + β of gender + (age [years] x β of age) + (height [m] x β of age)

Presented in numbers this is:

FVC = -3.62 + 0.179 - 1.070 + 0.692 + (38 x -0.014) + (1.78 x 4.12) = 2.98 l.

Longitudinal changes

FVC and FEV_1 increased in all four groups until one year after discharge from inpatient rehabilitation (Figures 1a, 1b). At discharge from inpatient rehabilitation FVC and FEV_1 were no more significantly lower than able bodied subjects' reference values, i.e. within able bodied subjects 95% confidence intervals, for all groups except HT (Figures 1a, 1b). In contrast, FIV_1, PEF and PIF generally seemed to remain constant during the first year after discharge from inpatient rehabilitation (Table 2; Figure 1c-1e). None of the four groups reached 100% of able bodied subjects' predicted values for PEF throughout the analyzed time-course. For FIV_1 and PIF, significant differences in time-courses between groups were found. During inpatient rehabilitation, FIV_1 increased significantly less in subjects with paraplegia (HP and LP) compared to subjects with tetraplegia (HT and LT) and PIF of the LP group increased significantly less than the other three groups (Table 2). Calculated estimates of Pe_{max} and Pi_{max} for subjects with para- and tetraplegia all remain below 100% of able bodied subjects' age- and gender-corrected reference values until one year after discharge from inpatient rehabilitation (Figure 2). Pi_{max} showed significant increases during and after inpatient rehabilitation, while Pe_{max} showed significant increases only in subjects with paraplegia during inpatient rehabilitation (Figure 2). P_{endu} significantly increased during, but not after inpatient rehabilitation. Estimates for t_{endu} did not change over time (Table 3).

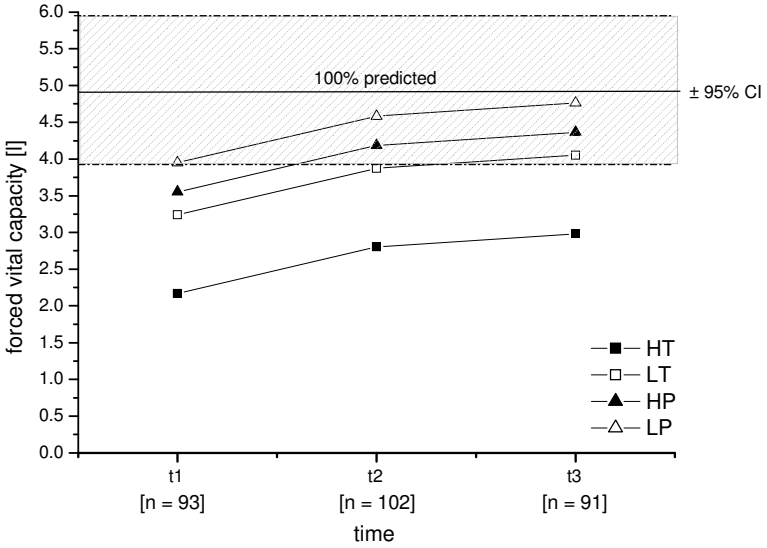

Figure 1a

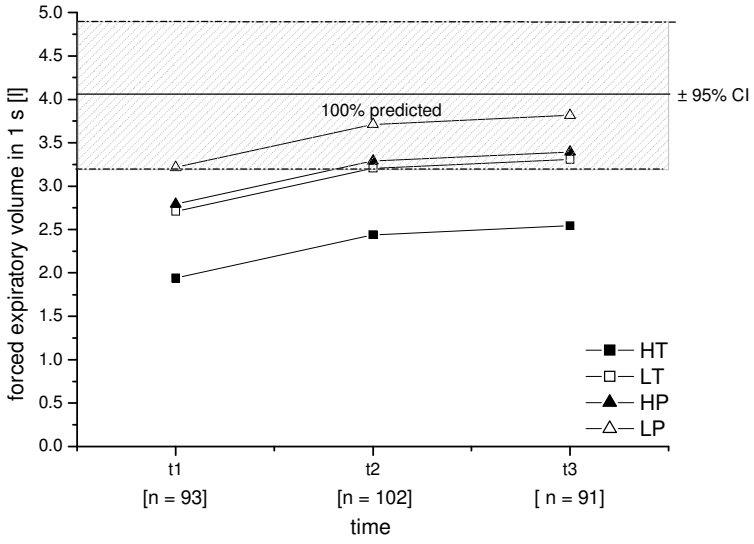

Figure 1b

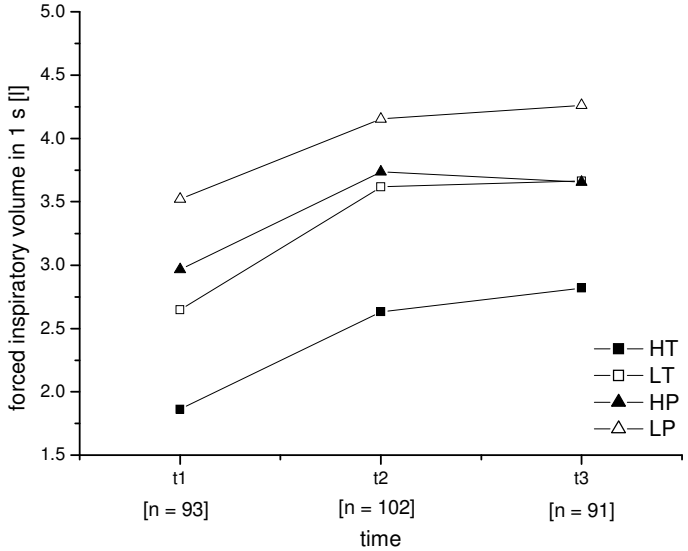

Figure 1c

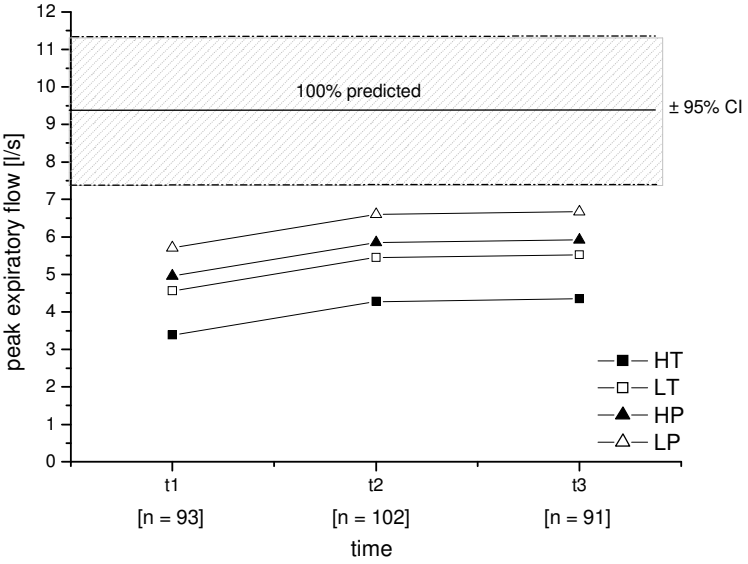

Figure 1d

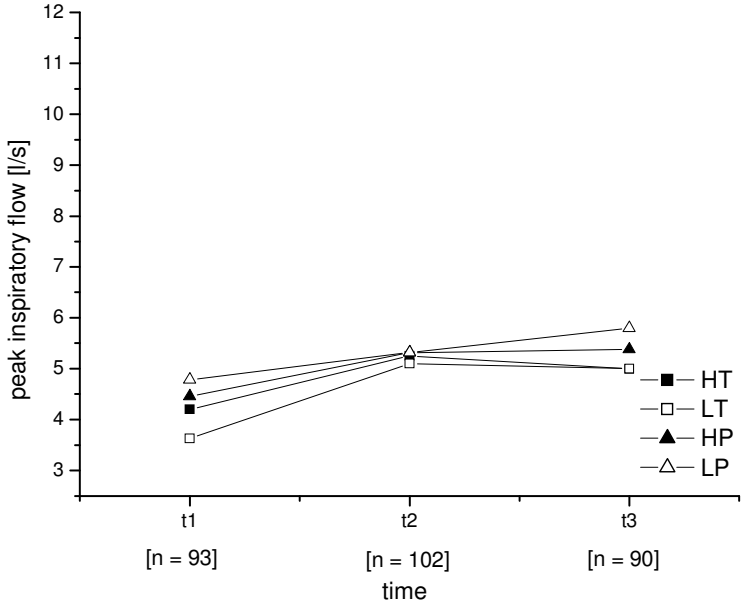

Figure 1e

Figures 1a - 1e: Calculated estimates from the final multilevel regression models for time-courses (t_1 = start of active rehabilitation, t_2 = end of inpatient rehabilitation, t_3 = one year after t_2) of lung function parameters (1a) forced vital capacity, 1b) forced expiratory volume in 1 s, 1c) forced inspiratory volume in 1 s, 1d) peak expiratory flow, 1e) peak inspiratory flow) for the four lesion level groups separately; HT = subjects with high tetraplegia (C3-C5), LT = subjects with low tetraplegia (C6-C8), HP = subjects with high paraplegia (T1-T6), LP = subjects with low paraplegia (T7-T12). Values were calculated for males with average age and height of the tested group. Age, gender and height corrected able bodied subjects reference values (100% predicted) with 95% confidence intervals (CI) are given for forced vital capacity, forced expiratory volume in 1 s, and peak expiratory flow.

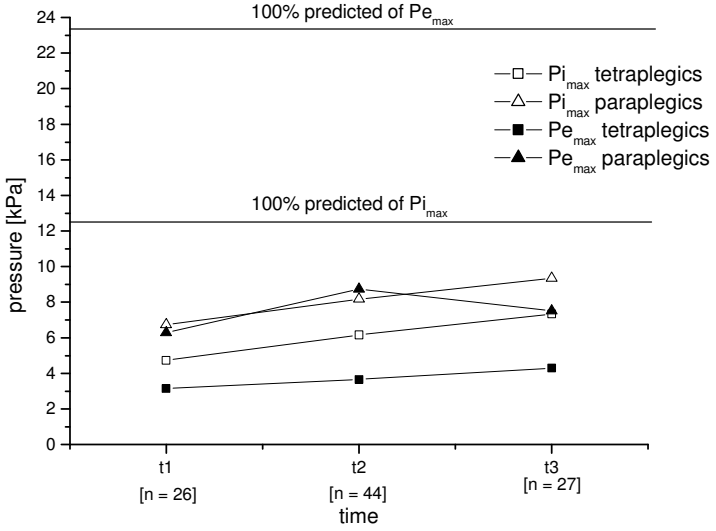

Figure 2: Calculated estimates from the final multilevel regression models for time-courses (t_1 = start of active rehabilitation, t_2 = end of inpatient rehabilitation, t_3 = one year after t_2) of inspiratory (Pi_{max}) and expiratory (Pe_{max}) muscle pressure generating capacity for men with paraplegia and tetraplegia

Influence of lesion level

HT showed significantly lower FVC, FEV_1, FIV_1 and PEF values than LT while these values were significantly higher for LP than LT (Figure 1a-1d). There were no significant differences between LT and HP in any of the tested lung function parameters (Table 2). $Pe_{max,}$ Pi_{max} and P_{endu} were lower in subjects with tetraplegia compared to subjects with paraplegia. There were significant differences in time-courses of Pe_{max} between subjects with paraplegia and subjects with tetraplegia, while Pe_{max} of subjects with tetraplegia did not change over time, Pe_{max} of subjects with paraplegia increased during inpatient rehabilitation but decreased thereafter (Figure 2). Estimates for t_{endu} showed no significant differences between groups (Table 3).

Table 2: Regression coefficients (β values) and standard errors (SE) for the final multilevel regression model describing effects of time, lesion and personal characteristics on the different lung function parameters [N = 109]

	FVC (l)		**FEV_1(l**		**FIV_1 (l)**		**PEF (l/s)**		**PIF (l/s)**	
	β	(SE)	**β**	(SE)	**β**	(SE)	**β**	(SE)	**β**	(SE)
constant	**-3.620**	(1.549)	**-2.485**	(1.338)	**-3.173**	(1.502)	**-2.612**	(2.644)	**-0.756**	(2.554)
Δt_2-t_1	**-0.632**	(0.080)*	**-0.498**	(0.062)*	**-0.971**	(0.162)*	**-0.891**	(0.127)*	**-1.472**	(0.290)*
Δt_2-t_3	**0.179**	(0.057)*	**0.103**	(0.046)*	**0.046**	(0.119)	**0.073**	(0.118)	**-0.096**	(0.278)
ΔHT-LT	**-1.070**	(0.235)*	**-0.768**	(0.206)*	**-0.785**	(0.245)*	**-1.173**	(0.376)*	**-0.898**	(0.438)*
ΔLT-HP	**0.311**	(0.226)	**0.085**	(0.187)	**0.119**	(0.241)	**0.399**	(0.418)	**0.155**	(0.413)
ΔLT-LP	**0.708**	(0.206)*	**0.505**	(0.171)*	**0.536**	(0.221)*	**1.152**	(0.395)*	**0.217**	(0.378)
gender	**0.692**	(0.192)*	**0.513**	(0.167)*	**0.472**	(0.183)*	**0.844**	(0.303)*	**0.920**	(0.317)*
age	**-0.014**	(0.005)*	**-0.021**	(0.005)*	**-0.012**	(0.005)*	n.s.		**-0.019**	(0.009)*
height	**4.120**	(0.908)*	**3.355**	(0.784)*	**3.694**	(0.880)*	**4.054**	(1.531)*	**3.178**	(1.495)*
Δt_1-t_2xHTLT	n.s.		n.s.		**0.200**	(0.219)	n.s.		**0.420**	(0.396)
Δt_1-t_2xHPLT	n.s.		n.s.		**0.399**	(0.204)*	n.s.		**0.614**	(0.369)
Δt_1-t_2xLPLT	n.s.		n.s.		**0.538**	(0.194)*	n.s.		**0.940**	(0.349)*
Δt_2-t_3xHTLT	n.s.		n.s.		**0.139**	(0.173)	n.s.		**-0.162**	(0.403)
Δt_2-t_3xHPLT	n.s.		n.s.		**0.074**	(0.157)	n.s.		**0.158**	(0.367)
Δt_2-t_3xLPLT	n.s.		n.s.		**0.263**	(0.143)	n.s.		**0.574**	(0.335)

FVC = forced vital capacity; FEV_1 forced expiratory volume in 1 s; FIV_1 = forced inspiratory volume in 1 s; PEF = peak expiratory flow; PIF = peak inspiratory flow; β = regression coefficient for each independent variable; SE = standard error of this regression coefficient; Δt_1-t_2 / Δt_2-t_3 = time dummies with t_2 as reference; HT = high tetraplegic; LT = low tetraplegic; HP = high paraplegic; LP = low paraplegic; ΔHT-LT / ΔLT-HP / ΔLT-LP = group dummies with LT as reference; gender: 0 = women; 1 = men; age = years; height = m; Δt_1-t_2xHTLT / Δt_1-t_2xHPLT / Δt_1-t_2xLPLT / Δt_2-t_3xHTLT / Δt_2-t_3xHPLT / Δt_2-t_3xLPLT = interaction terms time x group; * = significant influencing factor; n.s. not significant

Table 3: Regression coefficients (β values) and standard errors (SE) for the final multilevel regression model describing effects of time and personal characteristics on different parameters of respiratory muscle pressure generating capacity [n = 55]

	Pi_{max} (kPa)		**Pe_{max} (kPa)**		**P_{endu} (kPa)**		**t_{endu} (min)**	
	β	(SE)	**β**	(SE)	**β**	(SE)	**β**	(SE)
constant	**3.982**	(0.748)	**2.079**	(0.935)	**2.993**	(0.213)	**4.240**	(0.381)
Δt_2-t_1	**-1.444**	(0.387)*	**-0.508**	(0.759)	**-0.689**	(0.200)*	**-0.853**	(0.504)
Δt_2-t_3	**1.177**	(0.538)*	**0.645**	(0.716)	**0.090**	(0.198)	**-0.553**	(0.415)
lesion	**2.015**	(0.641)*	**5.078**	(0.988)*	**0.538**	(0.261)*	**0.409**	(0.370)
gender	**2.183**	(0.702)*	**1.583**	(0.753)*	n.s.		n.s.	
Δt_1-t_2 x lesion	n.s.		**-1.945**	(0.920)*	n.s.		n.s.	
Δt_2-t_3 x lesion	n.s.		**-1.874**	(0.916)*	n.s.		n.s.	

Pi_{max} = maximal inspiratory muscle pressure generating capacity; Pe_{max} = maximal expiratory muscle pressure generating capacity; P_{endu} = maximal pressure of inspiratory threshold endurance test; t_{endu} = time of inspiratory threshold endurance test; β = regression coefficient for each independent variable; SE = standard error of this regression coefficient; t_1 = start of active rehabilitation, t_2 = end of inpatient rehabilitation; t_3 = 1 year after discharge from inpatient rehabilitation; Δt_1-t_2 / Δt_2-t_3 = time dummies with t_2 as reference; lesion: 0 = tetraplegic, 1 = paraplegic; gender: 0 = women; 1 = men; Δt_1-t_2 x lesion, Δt_2-t_3 x lesion = interaction terms time x lesion; * = significant influencing factor; n.s. = not significant

Influence of personal factors

Personal factors such as gender, age and height had significant influences on most lung function parameters, with the exception of age having no influence on PEF, i.e. PEF was the only parameter which seems not to decrease with age. Body mass and smoking had no significant effect on any of the measured parameters (Table 2). Calculated age- and height-corrected able bodied subjects 100% predicted (95% CI of reference values) for men were 4.93 (3.93-5.93) l FVC, 4.06 (3.17-4.90) l FEV_1 and 9.44 (7.45-11.43) l/s PEF (Figures 1a, 1b, 1d). Pi_{max} and Pe_{max} were only influenced by gender which resulted in higher estimates for men than for women, while P_{endu} and t_{endu} were not influenced by any of the tested personal factors (Table 3).

Discussion

The most important finding of this study is that inspiratory and especially expiratory muscle pressure generating capacity is affected to a great extent after a SCI. Results clearly show that respiratory function improved with time during inpatient rehabilitation. Expiratory muscle

pressure generating capacity also increased during inpatient rehabilitation, but it already decreased during the first year after inpatient rehabilitation. Especially in subjects with tetraplegia, respiratory muscle pressure generating capacity should be screened and trained regularly after inpatient rehabilitation.

Longitudinal changes

This study showed that FVC, FEV_1 and Pi_{max} increased until one year after inpatient rehabilitation while FIV_1, PEF and PIF remained constant or even decreased (Pe_{max}) after inpatient rehabilitation. Interestingly, positive associations of Pi_{max} to FVC and FEV_1 were found in different studies (26, 45), which supports our findings of similar trajectories of these three parameters.

There are several factors which change over time after an acute SCI, such as changes in muscle tone, spasticity, a lower chest wall and a higher abdominal compliance (10, 23). Further, factors such as postural changes, trunk stabilisation and changes in physical activity levels are known to influence respiratory function and may therefore influence trajectories of respiratory function as well (12, 16, 44, 49). Increasing spasticity and chest wall stiffness occur over time in subjects with SCI (10, 23). Together with possible decreases in physical activity levels after inpatient rehabilitation, this may have avoided further increases in FIV_1, PEF, PIF and Pe_{max} between t_2 and t_3. The higher abdominal compliance especially in subjects with tetraplegia and high paraplegia changes functional residual capacity, since the diaphragm is less pushed up due to the missing tone of abdominal muscles (48). This on the one hand reduces inspiratory capacity and therefore FVC, FIV_1, PIF and Pi_{max}, but on the other hand also pulmonary recoil pressure of the diaphragm, which helps to improve expiratory muscle function, i.e. FEV_1, PEF, and Pe_{max} (29). Further, it is known that besides its function as a respiratory muscle, the diaphragm also acts as a trunk extensor and therefore supports trunk stabilization in subjects with tetraplegia (44). Therefore, a standardized measurement position is of vital importance.

Subjects with para- and tetraplegia showed significant improvements in P_{endu} only during inpatient rehabilitation. This may result from improvements of the general physical fitness due to physical activities performed during inpatient rehabilitation. Unfortunately there is no data available about the exact amount of physical exercise training during inpatient rehabilitation.

Influence of lesion level

As expected and already shown in earlier studies (20, 32, 33, 36), we also found significant influences of lesion level on lung function and respiratory muscle pressure generating

capacity in subjects with recent SCI; the higher the lesion level, the lower the respiratory function (Figures 1 and 2). Therefore, separate regression equations for subjects with SCI and especially for different lesion level groups, as presented in this paper, seem to be justified.

Fishburn et al. found increases in respiratory tract infections with increasing lesion levels (17). Further, respiratory tract infections seem to be associated with the ability to cough as well as with PEF and Pe_{max} (9, 17, 39). Coughing is important for airway clearance and prevention of pulmonary complications (24, 50). Fugl-Meyer further reported that a PEF of at least 5-6 l/s is necessary to produce an effective cough (19). Even if this is much below able bodied subjects 100% predicted values, our subjects with high tetraplegia did not reach this level throughout the whole analyzed time-course (Figure 1d). Therefore, subjects with a high motor complete tetraplegia seem to be at high risk for respiratory tract infections. For the optimization of cough capacity, inspiratory muscle function should be considered as well. A deep inspiration increases pulmonary recoil pressure and is therefore an important precondition of an effective cough (28).

Influence of personal factors

The influence of personal factors such as gender, age and height on respiratory function is generally known from able bodied subjects reference equations (6, 40). In the present study, gender had a significant effect on all lung function parameters, leading to 0.5-0.7 l higher FVC, FEV_1 und FIV_1 and 0.8-0.9 l/s higher PEF and PIF estimates for men than for women (Table 2). Gender differences in the able bodied population are somewhat higher for FVC (0.9 l) and PEF (2.1 l/s). However, relative to the lower values in subjects with SCI, gender differences seem to be quite similar (40). Regarding respiratory muscle pressure generating capacity, gender has a large effect in able bodied subjects (6) with 30% higher Pi_{max} and 38% higher Pe_{max} estimates for men than for women. In our Dutch SCI sample, gender even had a 5% higher effect on respiratory muscle pressure generating capacity than in able bodied subjects, resulting in differences of 35% for Pi_{max} and 43% for Pe_{max} (Table 3).

To our knowledge there are only few studies addressing issues regarding ageing and SCI (51). Furthermore, studies assessing the interaction of ageing and respiratory function in SCI are non existent. The influence of ageing on lung function, i.e. the decline in respiratory function with age, seems to be even lower in subjects with SCI (-0.012 to -0.021 l per year; Table 2) than in the able bodied population (-0.026 to -0.043 l per year) (40). Nevertheless, this study only assessed changes during the first two years after injury. To really get reliable data on influences of ageing on lung function for subjects with SCI, longitudinal studies of at least 10 years are needed.

Height only had, similar to able bodied subjects reference equations, significant influences on lung function, but not on respiratory muscle pressure generating capacity (Table 2). Keeping

in mind the absolute lower values of subjects with SCI, influences of height on lung function seem to be quite similar to the able bodied subjects population (40).

In accordance to able bodied subjects reference equations, body mass had no significant effect on any of the measured parameters, probably since most of our subjects were within the range of normal body mass index (Table 1). It is known that in obese able bodied subjects lung function is diminished (8, 11, 27). Nor former, neither current smoking had any significant effect on the tested lung function and respiratory muscle pressure generating capacity parameters. One possible reason for that finding could be that many subjects stopped smoking after SCI (Table 1). Results of two other studies provided equivocal findings concerning effects of smoking on lung function in SCI (2, 32).

Clinical relevance

The results of the present study clearly show that during inpatient rehabilitation lung function and respiratory muscle pressure generating capacity generally increase without specific respiratory muscle training but are on a very low level in subjects with high tetraplegia. Changes in muscle tone, spasticity, chest wall and abdominal compliance, body position and physical exercise training are factors that may additionally affect trajectories of respiratory function, especially during the initial time after injury. Individuals with high tetraplegia are those at the highest risk for respiratory complications, since they do not reach the lower limit to produce an effective cough. Therefore, regular screening and early training interventions in at least subjects with high, motor complete tetraplegia is important. Since the commonly used screening parameters FVC and FEV_1 are the least affected, especially PEF, Pe_{max} and Pi_{max} should also become part of regular lung function testing.

Conclusion

All estimates for lung function and maximal respiratory muscle pressure generating capacity showed significant increases during inpatient rehabilitation, but to a different extent. During the first year after discharge from inpatient rehabilitation, only FVC, FEV_1 and Pi_{max} further improved, while all other parameters remained constant or even decreased (Pe_{max}). Subjects with high tetraplegia generally showed the highest impairments while PEF and Pe_{max} were the most affected parameters in all groups of subjects with SCI. Thus, this study should motivate health care professionals to improve follow up measurements as well as patient-motivation and possibilities for training of the SCI population.

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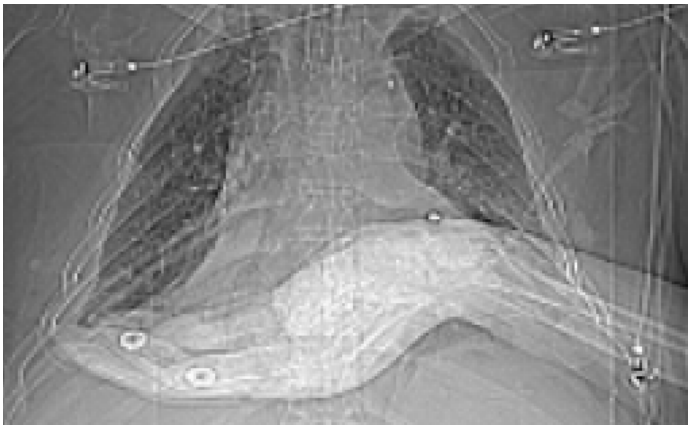
References

1. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 152: 1107-1136, 1995.
2. **Almenoff PL, Spungen AM, Lesser M, and Baumann WA**. Pulmonary function survey in spinal cord injury: influences of smoking and level and completeness of injury. *Lung* 173: 297-306, 1995.
3. **Anke A, Aksnes AK, Stanghelle JK, and Hjeltnes N**. Lung volumes in tetraplegic patients according to cervical spinal cord injury level. *Scand J Rehabil Med* 25: 73-77, 1993.
4. **Axen K, Pineda H, Shunfenthal I, and Haas F**. Diaphragmatic function following cervical cord injury: neurally mediated improvement. *Arch Phys Med Rehabil* 66: 219-222, 1985.
5. **Bach JR, and Wang TG**. Pulmonary function and sleep disordered breathing in patients with traumatic tetraplegia: a longitudinal study. *Arch Phys Med Rehabil* 75: 279-284, 1994.
6. **Black LF, and Hyatt RE**. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 99: 696-702, 1969.
7. **Bluechardt MH, Wiens M, Thomas SG, and Plyley MJ**. Repeated measurements of pulmonary function following spinal cord injury. *Paraplegia* 30: 768-774, 1992.
8. **Bottai M, Pistelli F, Di Pede F, Carrozzi L, Baldacci S, Matteelli G, Scognamiglio A, and Viegi G**. Longitudinal changes of body mass index, spirometry and diffusion in a general population. *Eur Respir J* 20: 665-673, 2002.
9. **Braun SR, Giovannoni R, and O'Connor M**. Improving the cough in patients with spinal cord injury. *Am J Phys Med* 63: 1-10, 1984.
10. **Brown R, DiMarco AF, Hoit JD, and Garshick E**. Respiratory dysfunction and management in spinal cord injury. *Respir Care* 51: 853-868;discussion 869-870, 2006.
11. **Chen Y, Horne SL, and Dosman JA**. Body weight and weight gain related to pulmonary function decline in adults: a six year follow up study. *Thorax* 48: 375-380, 1993.
12. **Cheng YJ, Macera CA, Addy CL, Sy FS, Wieland D, and Blair SN**. Effects of physical activity on exercise tests and respiratory function. *Br J Sports Med* 37: 521-528, 2003.
13. **de Groot S, Dallmeijer AJ, Post MW, van Asbeck FW, Nene AV, Angenot EL, and van der Woude LH**. Demographics of the Dutch multicenter prospective cohort study 'Restoration of mobility in spinal cord injury rehabilitation'. *Spinal Cord* 44: 668-675, 2006.
14. **De Troyer A, and Estenne M**. Functional anatomy of the respiratory muscles. *Clin Chest Med* 9: 175-193, 1988.
15. **DeVivo MJ, Black KJ, and Stover SL**. Causes of death during the first 12 years after spinal cord injury. *Arch Phys Med Rehabil* 74: 248-254, 1993.

16. **Estenne M, and De Troyer A**. Mechanism of the postural dependence of vital capacity in tetraplegic subjects. *Am Rev Respir Dis* 135: 367-371, 1987.
17. **Fishburn MJ, Marino RJ, and Ditunno JF, Jr.** Atelectasis and pneumonia in acute spinal cord injury. *Arch Phys Med Rehabil* 71: 197-200, 1990.
18. **Fugl-Meyer AR**. Effects of respiratory muscle paralysis in tetraplegic and paraplegic patients. *Scand J Rehabil Med* 3: 141-150, 1971.
19. **Fugl-Meyer AR**. The respiratory system. In: *Handbook of clinical Neurology*, edited by Vinken PJ, and Bruyn GW. New York: American Elsevier, 1976, p. 335-349.
20. **Fugl-Meyer AR, and Grimby G**. Ventilatory function in tetraplegic patients. *Scand J Rehabil Med* 3: 151-160, 1971.
21. **Garshick E, Kelley A, Cohen SA, Garrison A, Tun CG, Gagnon D, and Brown R**. A prospective assessment of mortality in chronic spinal cord injury. *Spinal Cord* 43: 408-416, 2005.
22. **Haas F, Axen K, Pineda H, Gandino D, and Haas A**. Temporal pulmonary function changes in cervical cord injury. *Arch Phys Med Rehabil* 66: 139-144, 1985.
23. **Hiersemenzel LP, Curt A, and Dietz V**. From spinal shock to spasticity: neuronal adaptations to a spinal cord injury. *Neurology* 54: 1574-1582, 2000.
24. **Irwin RS, Rosen MJ, and Braman SS**. Cough. A comprehensive review. *Arch Intern Med* 137: 1186-1191, 1977.
25. **Jackson AB, and Groomes TE**. Incidence of respiratory complications following spinal cord injury. *Arch Phys Med Rehabil* 75: 270-275, 1994.
26. **Jain NB, Brown R, Tun CG, Gagnon D, and Garshick E**. Determinants of forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC in chronic spinal cord injury. *Arch Phys Med Rehabil* 87: 1327-1333, 2006.
27. **Jones RL, and Nzekwu MM**. The effects of body mass index on lung volumes. *Chest* 130: 827-833, 2006.
28. **Kang SW, Kang YS, Sohn HS, Park JH, and Moon JH**. Respiratory muscle strength and cough capacity in patients with duchenne muscular dystrophy. *Yonsei Med J* 47: 184-190, 2006.
29. **Kang SW, Shin JC, Park CI, Moon JH, Rha DW, and Cho DH**. Relationship between inspiratory muscle strength and cough capacity in cervical spinal cord injured patients. *Spinal Cord* 44: 242-248, 2006.
30. **Karvonen J, Saarelainen S, and Nieminen MM**. Measurement of respiratory muscle forces based on maximal inspiratory and expiratory pressures. *Respiration; Int Rev Thoracic Dis* 61: 28-31, 1994.
31. **Ledsome JR, and Sharp JM**. Pulmonary function in acute cervical cord injury. *Am Rev Respir Dis*124: 41-44, 1981.
32. **Linn WS, Adkins RH, Gong H, Jr., and Waters RL**. Pulmonary function in chronic spinal cord injury: a cross-sectional survey of 222 southern California adult outpatients. *Arch Phys Med Rehabil* 81: 757-763, 2000.
33. **Linn WS, Spungen AM, Gong H, Adkins RH, Baumann WA, and Waters RL**. Forced vital capacity in two large outpatient populations with chronic spinal cord injury. *Spinal Cord* 39: 263-268, 2001.
34. **Loveridge B, Sanii R, and Dubo HI**. Breathing pattern adjustments during the first year following cervical spinal cord injury. *Paraplegia* 30: 479-488, 1992.
35. **Lucke KT**. Pulmonary management following acute SCI. *J Neurosci Nurs* 30: 91-104, 1998.
36. **Mateus SR, Beraldo PS, and Horan TA**. Cholinergic bronchomotor tone and airway caliber in tetraplegic patients. *Spinal Cord* 44: 269-274, 2006.
37. **McConnell AK, and Copestake AJ**. Maximum static respiratory pressures in healthy elderly men and women: issues of reproducibility and interpretation. *Respiration; Int Rev Thoracic Dis* 66: 251-258, 1999.
38. **McMichan JC, Michel L, and Westbrook PR**. Pulmonary dysfunction following traumatic quadriplegia. *JAMA* 243: 528-531, 1980.
39. **Polkey MI, Lyall RA, Green M, Nigel Leigh P, and Moxham J**. Expiratory muscle function in amyotrophic lateral sclerosis. *Am J Respir Crit Care Med* 158: 734-741, 1998.
40. **Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, and Yernault JC**. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 16: 5-40, 1993.

41. **Rasbash J, Browne W, Goldstein H, Yang M, Plewis I, Healy M, Woodhouse G, Draper D, Langford I, and Lewis T**. A User's Guide to MLwin. In: *Centre for Multilevel Modelling, Institute of Education, University of London*. London, United Kingdom: 2000.
42. **Roth EJ, Lu A, Primack S, Oken J, Nusshaum S, Berkowitz M, and Powley S**. Ventilatory function in cervical and high thoracic spinal cord injury. Relationship to level of injury and tone. *Am J Phys Med Rehabil / Assoc Acad Physiatr* 76: 262-267, 1997.
43. **Saltzstein R, and Melvin J**. Ventilatory compromise in spinal cord injury - a review. *J Am Paraplegia Soc* 9: 6-9, 1986.
44. **Sinderby C, Ingvarsson P, Sullivan L, Wickstrom I, and Lindstrom L**. The role of the diaphragm in trunk extension in tetraplegia. *Paraplegia* 30: 389-395, 1992.
45. **Sinderby C, Weinberg J, Sullivan L, Borg J, Lindstrom L, and Grassino A**. Diaphragm function in patients with cervical cord injury or prior poliomyelitis infection. *Spinal Cord* 34: 204-213, 1996.
46. **Syabbalo N**. Assessment of respiratory muscle function and strength. *Postgrad Med J* 74: 208-215, 1998.
47. **Twisk JW**. *Applied Longitudinal Data Analysis for Epidemiology, A Practical Guide*. Amsterdam: Cambridge University Press, 2003.
48. **Urmey W, Loring S, Mead J, Slutsky AS, Sarkarati M, Rossier A, and Brown R**. Upper and lower rib cage deformation during breathing in quadriplegics. *J Appl Physiol* 60: 618-622, 1986.
49. **Vidal J, Javierre C, Segura R, Lizarraga A, Barbany JR, and Perez A**. Physiological adaptations to exercise in people with spinal cord injury. *J Physiol Biochem* 59: 11-18, 2003.
50. **Wang AY, Jaeger RJ, Yarkony GM, and Turba RM**. Cough in spinal cord injured patients: the relationship between motor level and peak expiratory flow. *Spinal Cord* 35: 299-302, 1997.
51. **Weitzenkamp DA, Jones RH, Whiteneck GG, and Young DA**. Ageing with spinal cord injury: cross-sectional and longitudinal effects. *Spinal Cord* 39: 301-309, 2001.
52. **Winslow C, and Rozovsky J**. Effect of spinal cord injury on the respiratory system. *Am J Phys Med Rehabil / Assoc Acad Physiatr* 82: 803-814, 2003.



Chapter 4

Optimal Intensity for Respiratory Muscle Endurance Training in Patients with Spinal Cord Injury

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Abstract

Objective: Respiratory muscle endurance of able bodied persons, assessed by normocapnic hyperpnoea at 70% of their maximal voluntary ventilation, usually ranges from 10-20 min. The aim of this study was to find the level of ventilation that patients with paraplegia and tetraplegia can sustain for 10-20 min to later be used as the guideline for respiratory muscle endurance training.

Methods: Two groups, 8 patients with paraplegia and 6 patients with tetraplegia participated in this pilot study with crossover setting. Respiratory muscle endurance tests were performed at 3 different intensities of normocapnic hyperpnoea, i.e. 20, 40 and 60% maximal voluntary ventilation. Subjects performed partial rebreathing from a bag to assure normocapnia. Respiratory endurance was separately analyzed for patients with para- and tetraplegia.

Results: Mean respiratory endurance times were 46.0, 18.9 and 4.2 min at 20, 40 and 60% maximal voluntary ventilation in patients with tetraplegia and 51.8, 38.8 and 12.2 min in patients with paraplegia. The duration differed significantly at 60% maximal voluntary ventilation between groups.

Conclusion: Minute ventilation to perform respiratory muscle endurance training can be set around 40% of maximal voluntary ventilation for patients with tetraplegia and around 60% of maximal voluntary ventilation for patients with paraplegia as these levels can be sustained for 10-20 min.

Introduction

Complete spinal cord injury (SCI) results in diminished pulmonary function, due to paralysis of respiratory muscles depending on the lesion level (13). While persons with paraplegia lack abdominal muscle function and lesion-dependent also intercostal muscle function, persons with tetraplegia lack most of the expiratory and even some of the auxiliary inspiratory muscles (7). This may lead to faster fatigue of the respiratory pump in subjects with SCI during physical activity, as well as to a restricted pulmonary capacity (23). Furthermore, persons with SCI are generally at higher risk for progressive respiratory insufficiency compared to able bodied people (14). Pulmonary complications are a major cause of death, in particular for persons with tetraplegia surviving the first 6 months after the trauma (9). The fact that patients with SCI activate their remaining respiratory muscles in daily life less than able bodied persons, due to the lack of whole-body physical activity, may also explain the weakened respiratory system (20), particularly for persons with tetraplegia. Therefore, special attention should be given to the functioning and improvement of their respiratory pump.

Leith & Bradley (15) showed that respiratory muscle strength and endurance can be specifically increased by appropriate respiratory muscle training in able bodied subjects. So far, studies showing an improvement of respiratory muscle function in patients with SCI focussed on respiratory resistance or resistance endurance training (11, 12, 21, 28). However, for these patients, respiration causes major problems during physical activity (29) and for patients with tetraplegia even during the night (e.g. sleep apnoea) (5, 6, 18, 22). Therefore, respiratory endurance seems to be more critical than respiratory muscle strength. Sedentary as well as trained able bodied subjects (24) significantly increased the endurance of respiratory muscles as well as whole-body exercise endurance by means of normocapnic hyperpnoea training at 60-70% of their individual maximal voluntary ventilation (MVV). In view of these effects in able bodied subjects, normocapnic hyperpnoea training is expected to be even more beneficial for persons with weak respiratory muscles, such as people with SCI, but data is missing for this group.

Therefore, the first step to adapt normocapnic hyperpnoea training for persons with SCI is to test respiratory endurance in this group of subjects at different minute ventilations, i.e. different intensities. We hypothesize that, due to the partly lacking respiratory muscle mass, the minute ventilation that can be sustained for 10-20 min, an appropriate duration for normocapnic hyperpnoea training in this group of patients, will be higher for patients with paraplegia than for patients with tetraplegia. To test this hypothesis, patients with paraplegia as well as tetraplegia performed respiratory endurance tests by means of exhaustive normocapnic hyperpnoea at three different intensities.

Methods

Thirty-three patients, 22 with paraplegia and 11 with tetraplegia, who were hospitalized in a SCI rehabilitation center for first rehabilitation between September 2001 and July 2004, met the inclusion criteria (see below). Of these, 3 had no interest to participate and 16 were excluded according to the exclusion criteria (see below). Finally, 8 patients with paraplegia and 6 patients with tetraplegia were enrolled in the study. Characteristics of these subjects are shown in Table 1. Inclusion criteria were age between 18 and 45 years with an acute traumatic, motor complete lesion (ASIA A or B). Exclusion criteria were asthma, chronic obstructive pulmonary disease, pneumonia, tracheotomy, bronchial or urinary infections, irregular medication, peanut or latex allergy and epilepsy. In order to reach more or less stable ventilatory function after injury, we enrolled patients with paraplegia 4 to 6 months after injury and patients with tetraplegia 6 to 8 months after injury (1, 16). Prior to the start of the study, all patients were informed in detail and gave their written informed consent. The ethics committee of the canton Lucerne, Switzerland approved the study.

Table 1: Characteristics of patients with paraplegia and tetraplegia

sex	**age** [years]	**height** [m]	**weight** [kg]	**TPI** [mt]	**lesion level**	**smoker**
paraplegia						
m	30	1.80	75	6	T4	no
m	22	1.78	62	4	T5	no
w	26	1.68	53	4	T5/6	no
m	23	1.98	83	4	T6	yes
m	39	1.70	80	5	T10	no
m	26	1.82	72	4	T11	no
m	32	1.85	70	4	T11	no
m	45	1.78	73	4	L1	no
Mean ± SD	**31 ± 8**	**1.80 ± 0.09**	**71 ± 10**	**4 ± 1**		
tetraplegia						
w	22	1.73	52	7	C4	no
w	39	1.53	41	6	C5	no
m	21	1.87	70	6	C6	no
m	21	1.83	59	7	C7	yes
m	22	1.75	69	7	C7	no
m	22	1.72	58	6	C7	no
Mean ± (SD)	**25 ± 7**	**1.74 ± 0.12**	**58 ± 11**	**7 ± 1**		

TPI = time post injury; mt = month; m = man; w = woman; C = cervical lesion; T = thoracic lesion; L = lumbar lesion; SD = standard deviation

Equipment

Vital capacity (VC), peak inspiratory and expiratory flows (PIF, PEF), forced in- and expiratory volumes in 1 s (FIV_1, FEV_1) and MVV over 12 s were measured by a metabolic chart (Oxycon α, Jaeger, Hoechberg, Germany), using a turbine for volume measurements and fast-responding gas analysers. The system had been calibrated with a 3-litre syringe and certified mixed calibration gas before each test. Maximal inspiratory and expiratory pressures (Pi_{max}, Pe_{max}) were measured by a hand-held mouth pressure meter (Micro MPM, Micro Medical Ltd, Chatham Kent, UK) including a small air leak to prevent glottis closure.

Respiratory muscle endurance tests, i.e. normocapnic hyperpnoea to exhaustion, were performed using a special partial rebreathing device (SpiroTiger, idiag AG, Fehraltorf, Switzerland) providing target respiratory frequency and tidal volume. During respiratory muscle endurance tests, end-tidal CO_2 partial pressure and ventilatory variables were monitored and recorded breath by breath (Oxycon α, Jaeger, Hoechberg, Germany) to verify normocapnia and target ventilation. Heart rate was measured by oximetry (OxyTip, Datex-Ohmeda 3900, Louisville, USA) on the right middle finger and blood pressure by plethysmography (Finapress blood pressure Monitor, Ohmeda 2300, BOC Healthcare, Englewood, Colorado, USA) on the left middle finger, placing the left forearm on heart level (see Figure 1 for experimental setup). Blood samples (20 µl) were drawn from an earlobe and analyzed for blood lactate concentration enzymatically (Super GL Ambulance, Ruhrtal Labor Technik, Moehnesee, Germany). Perception of breathlessness and respiratory effort were indicated by the subjects at rest and at the end of each test on a visual analogue scale ranging from 0 to 10.

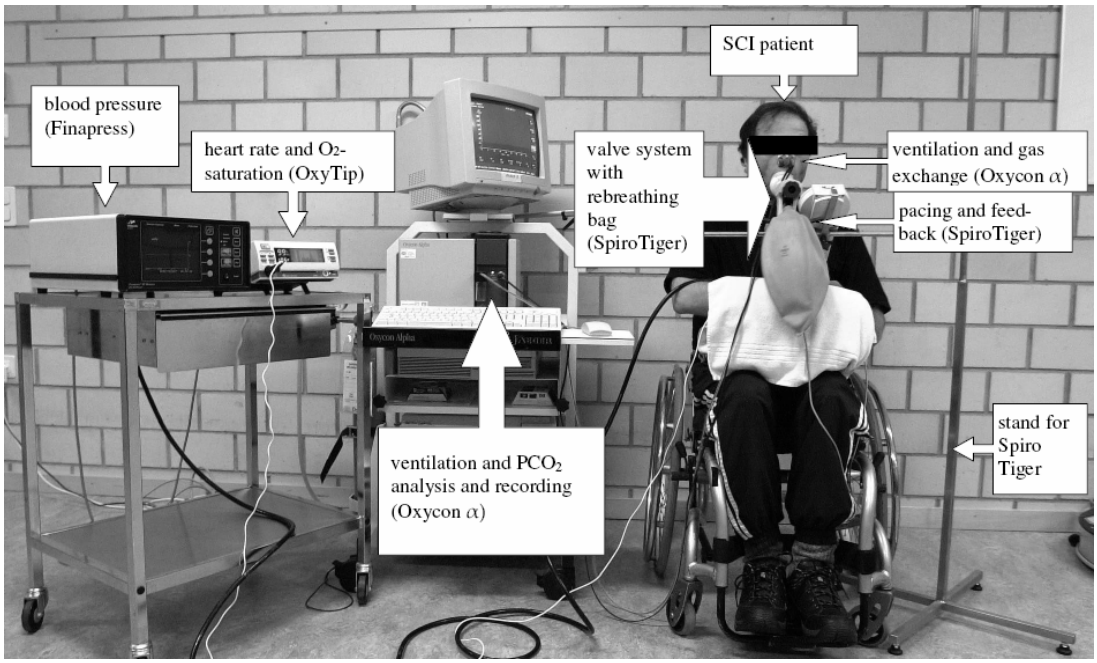

Figure 1: Experimental setup

Protocol

Every patient reported six times to the laboratory, with an interval between visits of at least 72 h. During the first three sessions, lung function as well as Pi_{max} (from residual volume) and Pe_{max} (from total lung capacity), both measures of respiratory muscle strength, were assessed. Each measurement was repeated three to six times until values did not differ more than ± 5%. The best effort within these limits was recorded. All respiratory measurements were conducted according to the spirometry testing standards in SCI (13) in an upright sitting position in the patient's own wheelchair. After lung function and respiratory muscle strength measurements, the normocapnic hyperpnoea training device was adjusted to one of the three intensities corresponding to 20, 40 or 60% of each patient's individual MVV. Subjects were then familiarised with the technique to perform normocapnic hyperpnoea and they were also trained to use the visual analogue scale.

During the last three sessions, subjects performed one respiratory muscle endurance test each day at 20, 40 or 60% of their MVV, in random order. During respiratory muscle endurance test sessions, they were verbally encouraged to keep the target minute ventilation (V_E) of the corresponding intensity. The test was stopped either by the patient due to exhaustion or by the experimenter, if V_E was more than 5 l/min lower than the target value for more than 30 s or if the test duration reached 60 min. Patients had to abstain from caffeine 24 h before each test. Information about nutrition, sleep, physical activity and medication 24 h prior to each test were collected by a questionnaire.

Heart rate and blood pressure were registered at rest, every 2 min during and at the end of each test. Blood samples for blood lactate analyses were drawn at the same timepoints. Blood pressure measurements were performed in patients with paraplegia only, as sympathetic activity regulating blood pressure is absent in patients with tetraplegia and thus blood pressure is influenced by other factors (e.g. micturition) causing random fluctuations (26).

Statistics

Between-group differences in respiratory muscle endurance, absolute V_E during respiratory muscle endurance tests, breathlessness, respiratory effort, heart rate, blood pressure and blood lactate concentration, were tested using Wilcoxon's rank sum tests. Systolic vs. diastolic increases in blood pressure between rest and test break off were also tested with Wilcoxon's rank sum tests. The Friedman two-way analysis of variance was used to assess within-group differences of respiratory muscle endurance test variables between tests at the three different intensities. For heart rate, blood pressure, breathlessness and respiratory effort, differences between rest and test break off were calculated for further analyses. Significance was accepted at $p < 0.05$. Statistical analyses were performed with a computer software package

(Systat, Version 10.2; Systat Software Inc.; Point Richmond, CA, USA). Values are presented as mean ± SD.

Results

Spirometry and respiratory muscle strength

Lung function and respiratory muscle strength of patients with para- and tetraplegia are presented in Table 2. All variables were significantly higher in patients with paraplegia compared to patients with tetraplegia.

Table 2: Lung function and respiratory muscle strength for patients with para- and tetraplegia presented as mean ± standard deviation

	patients with paraplegia	**patients with tetraplegia**	**p value**
VC (% pred)	100.5 ± 22.4	59.3 ± 21.9	0.007
FEV_1 (% pred)	100.9 ± 22.6	58.2 ± 18.6	0.007
FIV_1 (% pred)	104.8 ± 26.3	60.8 ± 21.5	0.012
PEF (% pred)	106.5 ± 23.5	57.0 ± 12.0	0.002
MVV (% pred)	127.4 ± 32.7	68.0 ± 19.0	0.003
Pi_{max} (% pred)	81.4 ± 14.6	59.0 ± 14.4	0.010
Pe_{max} (% pred)	42.3 ± 18.1	20.7 ± 5.5	0.004

VC = vital capacity; FEV_1 = forced expiratory volume in 1 s; FIV_1 = forced inspiratory volume in 1 s; PEF = peak expiratory flow; MVV = maximal voluntary ventilation; Pi_{max} = maximal inspiratory pressure; Pe_{max} = maximal expiratory pressure

Respiratory muscle endurance test: duration and respiratory assessments

Respiratory muscle endurance test duration at 60% MVV was significantly higher in patients with paraplegia compared to patients with tetraplegia being 12.2 ± 9.0 vs. 4.2 ± 3.4 min (Figure 2).

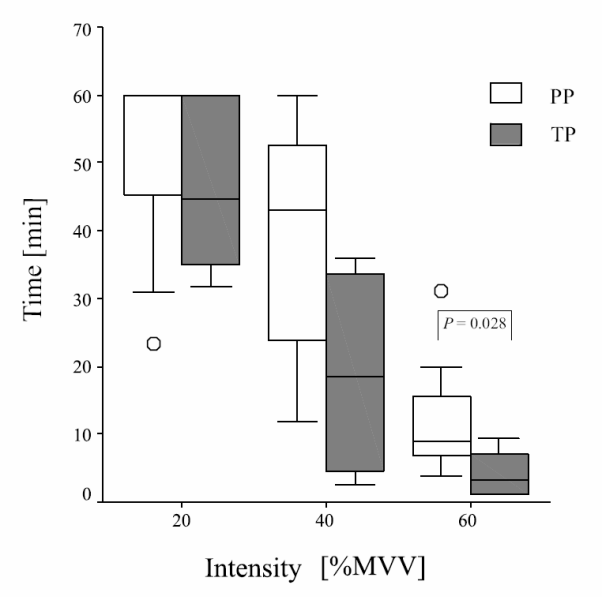

Figure 2: Median (lines inside boxes) and lower and upper quartiles (lower and upper edge of boxes) and range (whiskers) for duration of respiratory endurance test at different intensities for patients with paraplegia (PP) and for patients with tetraplegia (TP). MVV = maximal voluntary ventilation, O = outlier

Durations of respiratory muscle endurance tests at 40% MVV (38.8 vs. 18.9 min; p = 0.053) and 20% MVV (51.8 vs. 46.0 min; p = 0.391) did not differ significantly between groups. Within groups, respiratory muscle endurance test durations were significantly different between intensities (p = 0.006 for both groups). At 20% MVV, 6 patients with paraplegia and 2 patients with tetraplegia were stopped by the experimenter as they reached 60 min. Due to the higher absolute MVV of patients with paraplegia, their average V_E during respiratory muscle endurance tests was significantly higher at 20%, 40% and 60% MVV compared to patients with tetraplegia (Figure 3). Within both groups, V_E was significantly different between intensities ($p < 0.001$ for patients with paraplegia and $p = 0.007$ for patients with tetraplegia).

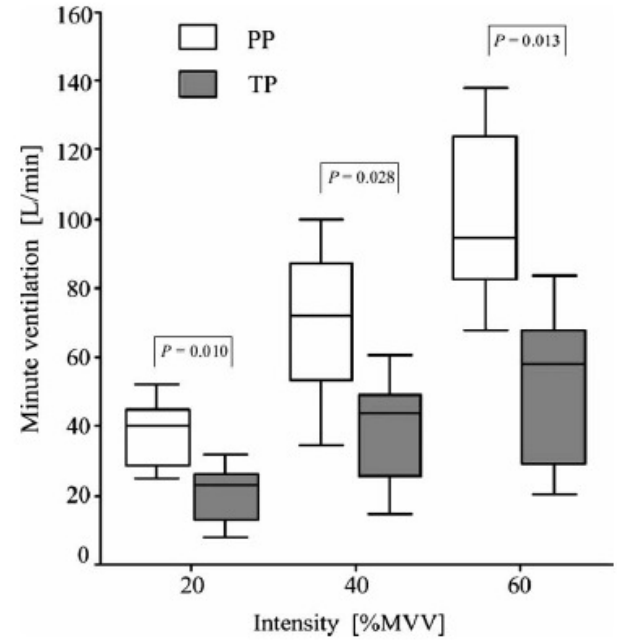

Figure 3: Median (lines inside boxes) and lower and upper quartiles (lower and upper edge of boxes) and range (whiskers) of minute ventilation during respiratory endurance tests at different intensities for patients with paraplegia (PP) and for patients with tetraplegia (TP). MVV = maximal voluntary ventilation

Perception of breathlessness did not differ between intensities for patients with paraplegia and tetrapelgia (p = 0.159 and p = 0.449). In patients with paraplegia, perception of respiratory effort was significantly higher at the end of respiratory muscle endurance tests at 60% (p = 0.005) and 40% (p = 0.034) MVV than at the end of the respiratory muscle endurance test at 20% MVV while it did not differ between intensities in patients with tetraplegia (p = 0.368) (Table 3).

Respiratory muscle endurance test: cardiovascular measurements

At rest, mean heart rate was 91 ± 12 bpm in patients with paraplegia and 74 ± 14 bpm in patients with tetraplegia. While blood pressure was not assessed in patients with tetraplegia (for details please see methods), in patients with paraplegia resting systolic blood pressure was 134 ± 28 mmHg and diastolic blood pressure was 74 ± 11 mmHg. Increases in systolic blood pressure between intensities were not significantly different (p = 0.159). Diastolic blood pressure increased significantly more during respiratory muscle endurance tests at 60% compared to 20% MVV (p = 0.005) and during 60% compared to 40% MVV (p = 0.034). Increases in diastolic blood pressure between 20% and 40% MVV were not significantly different (Table 3). Furthermore, at 60% MVV the increase in systolic blood pressure, was significantly larger than the increase in diastolic blood pressure (p = 0.012) while increases in systolic vs. diastolic blood pressure did not differ at 40% (p = 0.483) and 20% MVV (p = 0.726).

Table 3: Differences (Δ) between rest and end of respiratory endurance tests at different intensities for patients with para- and tetraplegia presented as mean ± SD.

Intensity (%MVV)	**patients with paraplegia** [n = 8]			**patients with tetraplegia** [n = 6]		
	20%	**40%**	**60%**	**20%**	**40%**	**60%**
Δ **heart rate** (bpm)	11±11	30±14	32±22	20±17	34±19	24±16
Δ **systolic blood pressure** (mmHg)	11.6±24.5	24.1±24.3	43.1±18.1°	NA	NA	NA
Δ **diastolic blood pressure** (mmHg)	14.1±10.5	16.9±9.7	23.3±12.9*†	NA	NA	NA
Δ **breathlessness** (points)	5.0±3.3	4.4±3.2	5.6±3.8	2.6±3.6	3.0±3.4	3.4±3.3
Δ **respiratory effort** (points)	4.1±2.5	7.2±3.1	9.0±1.8*†	6.7±3.0	7.9±2.9	7.9±1.7

Symbols: * Significant difference to 20% MVV;† Significant difference to 40% MVV;° Significant difference to Δ diastolic blood pressure at the same intensity. Note that there were no significant differences between groups of para- and tetrapelgic patients. Abbreviations: MVV = maximal voluntary ventilation; NA = not applicable

Respiratory muscle endurance test: blood lactate concentration

Blood lactate concentrations of the 3 tests are shown in Figure 4A for patients with paraplegia and Figure 4B for patients with tetraplegia. In patients with paraplegia, blood lactate concentrations during as well as at the end of respiratory muscle endurance tests decreased significantly compared to resting levels at 20% MVV ($p = 0.005$) as well as at 40% MVV ($p = 0.034$). At 60% MVV, blood lactate concentration did not change throughout the test (Figure 4A). In patients with tetraplegia, blood lactate concentrations decreased significantly compared to resting values during as well as at the end of the respiratory muscle endurance test at 20% MVV only ($p = 0.014$). At 40% and 60% MVV, blood lactate concentration did not change throughout the test (Figure 4B). Blood lactate concentrations did not differ between groups at identical intensities ($p = 0.180$ - 0.564).

Figure 4 A **Figure 4 B**

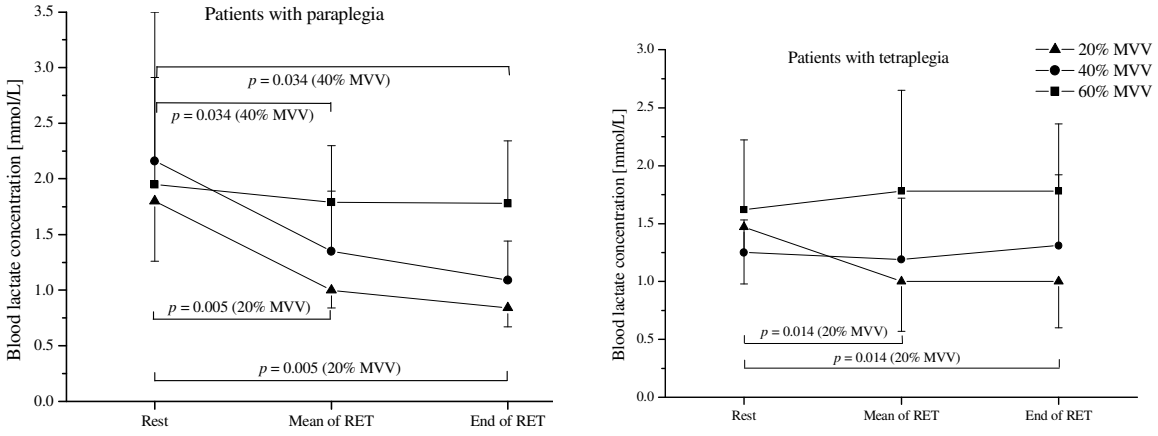

Figure 4: Time-course of blood lactate concentration (mean and SD) in **A)** patients with paraplegia and **B)** patients with tetraplegia at different intensities of the respiratory endurance tests (RET). MVV = maximal voluntary ventilation

Discussion

Respiratory muscle endurance and optimal training intensity

This study confirms our hypothesis that respiratory muscle endurance is reduced in patients with SCI compared to able bodied subjects, more so with higher lesion levels. While able bodied subjects can breathe for 30 min at > 60% of their individual MVV (2, 3, 25), patients with paraplegia only sustained this intensity for an average of 12.2 min while patients with tetraplegia only reached 4.2 min on average. Thus, when aiming for normocapnic hyperpnoea training durations of 10-20 min (as proven feasible for respiratory training in this group of

patients) (8, 12, 17, 21, 27, 28), V_E can be set around 60% MVV for patients with paraplegia but needs to be reduced to around 40% MVV for patients with tetraplegia. Although the perception of breathlessness was quite similar at the end of all tests in both groups, motivation to perform respiratory muscle endurance tests may also have influenced performance in these patients with SCI, shown by rather large inter-individual differences of respiratory muscle endurance test durations at given intensities. The above-mentioned guidelines should therefore be taken as starting levels in order to adjust the individual optimal training intensity.

It is noteworthy that respiratory endurance of patients with SCI is decreased compared to able bodied subjects, although the V_E values were based on individual subjects' MVV (19). For patients with tetraplegia, MVV was significantly below that of able bodied subjects. The decreased endurance may reflect a certain degree of muscle atrophy, occurring due to the immobilisation of the patients during the first weeks after injury (4). Furthermore, in patients with SCI, breathing and thus respiratory muscles are stimulated only little during daily activities due to the smaller muscle mass available compared to able bodied persons that are walking, running and lifting objects (20). In addition, the potential of shifting between the uses of different respiratory muscles allowing some recovery at sub-maximal ventilations is reduced.

Lung function and respiratory muscle strength

While lung function of patients with paraplegia was similar to able bodied subjects, respiratory muscle strength was lower than normal with Pi_{max} being around 20% and Pe_{max} around 60% lower than predicted from values assessed in able bodied persons. In patients with tetraplegia, however, lung function and inspiratory muscle strength were reduced to about 60% of predicted while expiratory muscle strength was only around 20% predicted. As hyperpnoea consists of repeated forced in- and expirations, maximal strength of these muscles (and the loss of it in the course of the task) is likely a factor affecting endurance as well. This assumption is supported by the fact that respiratory muscle endurance was reduced in subjects with paraplegia in the presence of reduced muscle strength and despite normal lung function, including FIV_1, FEV_1 and MVV.

Cardiovascular responses to respiratory muscle endurance tests

While blood pressure was not assessed in patients with tetraplegia due to the sympathetic autonomic impairment at this lesion level (10), both systolic and diastolic blood pressure increased significantly in patients with paraplegia during respiratory muscle endurance tests with a tendency to larger changes with increasing V_E. Also, systolic blood pressure increased to a larger extent than diastolic blood pressure at 60% MVV, suggesting that stroke volume increased during this task. This cardiovascular challenge, in particular during breathing at

60% MVV, strongly suggests that respiratory endurance training at this intensity will result in significant training effects.

Blood lactate metabolism

Interestingly, blood lactate concentrations decreased during respiratory muscle endurance tests at 20% and 40% MVV for patients with paraplegia and at 20% MVV for patients with tetraplegia, likely meaning that working muscles increasingly consumed blood lactate as an energy source. This shift in the balance of lactate production vs. consumption relative to resting conditions may result from the increased activity of respiratory muscles also using blood lactate as a fuel and/or the increased activity of the heart muscle, one of the major blood lactate consumers. The fact that blood lactate did not change during breathing at 60% MVV in patients with paraplegia and at 40% and 60% in patients with tetraplegia shows, in turn, that anaerobic metabolism was increasingly needed to achieve the work, also showing that patients with tetraplegia reached this limit 'earlier', i.e. at a lower intensity than patients with paraplegia. This, in turn, supports our previous suggestion that the higher the lesion, the smaller the ability of the still innervated respiratory muscles to share the work and to recover in-between. The continuous work then likely results in a faster development of fatigue and the necessity to recruit fast twitch fibres running on anaerobic metabolism.

These metabolic changes during respiratory muscle endurance tests together with the cardiovascular changes observed suggest that respiratory muscle endurance training - if performed in form of normocapnic hyperpnoea training at 60% MVV (patients with paraplegia) and 40% (patients with tetraplegia) - will result in significant training effects, e.g. increased respiratory muscle endurance likely accompanied by increased aerobic metabolism. Increased respiratory muscle endurance will, in turn, not only reduce the sensation of breathlessness during tasks of heavy breathing, e.g. driving uphill, but also the shift towards increased aerobic metabolism (as observed in able bodied after this kind of training (25)) might help to reduce early arm muscle fatigue resulting from intramuscular acidosis. In addition, lung function of patients with tetraplegia is likely to improve, which would then result in improved airway clearance and reduction of pulmonary complications.

In conclusion, this study showed that respiratory muscle endurance of patients with tetraplegia is reduced compared to patients with paraplegia. The optimal intensity for patients with SCI to perform normocapnic hyperpnoea training for 10-20 min should be set at V_E around 60% MVV for patients with paraplegia and around 40% MVV for patients with tetraplegia. Due to inter-individual differences, however, this intensity should then be adapted individually using the above mentioned values as guidelines.

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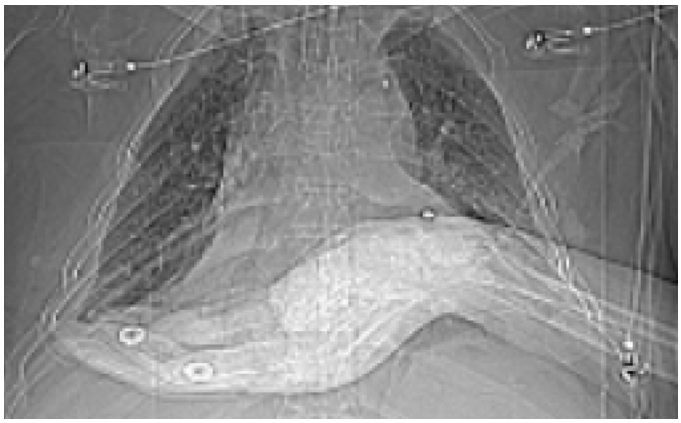
References

1. **Anke A, Aksnes AK, Stanghelle JK, and Hjeltnes N**. Lung volumes in tetraplegic patients according to cervical spinal cord injury level. *Scand J Rehabil Med* 25: 73-77, 1993.
2. **Boutellier U, Buchel R, Kundert A, and Spengler C**. The respiratory system as an exercise limiting factor in normal trained subjects. *Eur J Appl Physiol Occup Physiol* 65: 347-353, 1992.
3. **Boutellier U, and Piwko P**. The respiratory system as an exercise limiting factor in normal sedentary subjects. *Eur J Appl Physiol Occup Physiol* 64: 145-152, 1992.
4. **Burnham R, Martin T, Stein R, Bell G, MacLean I, and Steadward R**. Skeletal muscle fibre type transformation following spinal cord injury. *Spinal Cord* 35: 86-91, 1997.
5. **Burns SP, Kapur V, Yin KS, and Buhrer R**. Factors associated with sleep apnea in men with spinal cord injury: a population-based case-control study. *Spinal Cord* 39: 15-22, 2001.
6. **Burns SP, Little JW, Hussey JD, Lyman P, and Lakshminarayanan S**. Sleep apnea syndrome in chronic spinal cord injury: associated factors and treatment. *Arch Phys Med Rehabil* 81: 1334-1339, 2000.
7. **De Troyer A, and Estenne M**. Functional anatomy of the respiratory muscles. *Clin Chest Med* 9: 175-193, 1988.
8. **Derrickson J, Cielsa N, Simpson N, and Imle PC**. A comparison of two breathing exercise programs for patients with quadriplegia. *Phys Ther* 72: 763-769, 1992.
9. **DeVivo MJ, Black KJ, and Stover SL**. Causes of death during the first 12 years after spinal cord injury. *Arch Phys Med Rehabil* 74: 248-254, 1993.
10. **Figoni SF**. Exercise responses and quadriplegia. *Med Sci Sports Exerc* 25: 433-441, 1993.
11. **Gross D, Ladd HW, Riley EJ, Macklem PT, and Grassino A**. The effect of training on strength and endurance of the diaphragm in quadriplegia. *Am J Med* 68: 27-35, 1980.
12. **Huldtgren AC, Fugl-Meyer AR, Jonasson E, and Bake B**. Ventilatory dysfunction and respiratory rehabilitation in post-traumatic quadriplegia. *Eur J Respir Dis* 61: 347-356, 1980.
13. **Kelley A, Garshick E, Gross ER, Lieberman SL, Tun CG, and Brown R**. Spirometry testing standards in spinal cord injury. *Chest* 123: 725-730, 2003.
14. **Lanig I, and Peterson W**. The respiratory system in spinal cord injury. In: *Physical Medicine and Rehabilitation Clinics of North America; Topics in Spinal Cord Injury Medicine*, edited by Kraft G. Philadelphia: W:B: Saunders Company, 2000, p. 29-43.
15. **Leith DE, and Bradley M**. Ventilatory muscle strength and endurance training. *J Appl Physiol* 41: 508-516, 1976.
16. **Liaw MY, Lin MC, Cheng PT, Wong MK, and Tang FT**. Resistive inspiratory muscle training: its effectiveness in patients with acute complete cervical cord injury. *Arch Phys Med Rehabil* 81: 752-756, 2000.
17. **Loveridge B, Badour M, and Dubo H**. Ventilatory muscle endurance training in quadripegia: Effects on breathing pattern. *Paraplegia* 27: 329-339, 1989.
18. **McEvoy RD, Mykytyn I, Sajkov D, Flavell H, Marshall R, Antic r, and Thornton AT**. Sleep apnoea in patients with quadriplegia. *Thorax* 50: 613-619, 1995.
19. **McMahon ME, Boutellier U, Smith RM, and Spengler CM**. Hyperpnoea training attenuates peripheral chemosensitivity and improves cycling endurance. *J Exp Biol* 205: 3937-3943, 2002.
20. **Monroe MB, Tataranni PA, Pratley R, Manore MM, Skinner JS, and Ravussin E**. Lower daily energy expenditure as measured by a respiratory chamber in subjects with spinal cord injury compared with control subjects. *Am J Clin Nutr* 68: 1223-1227, 1998.

21. **Rutchik A, Weissman AR, Almenoff PL, Spungen AM, Bauman WA, and Grimm DR**. Resistive inspiratory muscle training in subjects with chronic cervical spinal cord injury. *Arch Phys Med Rehabil* 79: 293-297, 1998.
22. **Sajkov D, Marshall R, Walker P, Mykytyn I, McEvoy RD, Wale J, Flavell H, Thornton AT, and Antic R**. Sleep apnoea related Hypoxia is associated with cognitive disturbances in patients with tetraplegia. *Spinal Cord* 36: 231-239, 1998.
23. **Silva AC, Neder JA, Chiurciu MV, Pasqualin DC, da Silva RC, Fernadez AC, Lauro FA, de Mello MT, and Tufik S**. Effect of aerobic training on ventilatory muscle endurance of spinal cord injured men. *Spinal Cord* 36: 240-245, 1998.
24. **Spengler CM, and Boutellier U**. Breathless legs? Consider training your respiration. *News Physiol Sci* 15: 101-105, 2000.
25. **Spengler CM, Roos M, Laube SM, and Boutellier U**. Decreased exercice blood lactate concentrations after respiratory endurance training in humans. *Eur J Appl Physiol Occup Physiol* 79: 299-305, 1999.
26. **Teasell RW, Arnold JM, Krassioukov A, and Delaney GA**. Cardiovascular consequences of loss of supraspinal control of the sympathetic nervous system after spinal cord injury. *Arch Phys Med Rehabil* 81: 506-516, 2000.
27. **Uijl SG, Houtman S, Folgering HT, and Hopman MT**. Training of respiratory muscles in individuals with tetraplegia. *Spinal Cord* 37: 575-579, 1999.
28. **Wang TG, Wang YH, Tang FT, Lin KH, and Lien IN**. Resistive inspiratory muscle training in sleep-disordered breathing of traumatic tetraplegia. *Arch Phys Med Rehabil* 83: 491-496, 2002.
29. **Wien MF, Garshick E, Tun CG, Lieberman SL, Kelley A, and Brown R**. Breathlessness and exercise in spinal cord injury. *J Spinal Cord Med* 22: 297-302, 1999.



Chapter 5

Effects of Respiratory Muscle Endurance Training on Wheelchair Racing Performance in Athletes with Paraplegia: A Pilot Study

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Abstract

Objective: Respiratory muscle endurance training has been shown to improve both, respiratory muscle endurance and cycling exercise time at the anaerobic threshold in able bodied subjects. Since effects of respiratory muscle endurance training on upper extremity exercise performance have not yet been investigated, we evaluated the effects of respiratory muscle endurance training on 10 km time-trial performance in wheelchair-racing athletes.

Methods: 12 competitive wheelchair racing athletes participated in this pilot study. Two matched-pair groups were built according to subjects' lesion level. The training group (T) performed 30 sessions of respiratory muscle endurance training during 30 min each. The control group (C) did no respiratory muscle training. Differences in 10 km time-trial performance pre- vs. post- intervention were the main outcome measure.

Results: In T, the time on the 10 km time-trial decreased significantly pre- vs. post-intervention (27.1 ± 9.0 vs. 24.1 ± 6.6 min); this did not occur in C (23.3 ± 2.8 vs. 23.2 ± 2.4 min). No between groups difference was present ($p = 0.150$). Respiratory muscle endurance increased significantly within T (9.1 ± 7.2 vs. 39.9 ± 17.8 min) and between groups, but not within C (4.3 ± 2.9 vs. 6.6 ± 7.0 min) pre- vs. post intervention. VO_{2peak} showed no significant within- nor between-groups differences. Expiratory muscle strength increased significantly within T ($p = 0.028$) but not within C and nor between groups.

Conclusion: Six weeks of respiratory muscle endurance training enhanced respiratory muscle endurance. There was a strong trend with a large observed effect size of $d = 0.87$, towards improved performance in the 10 km time-trial after six weeks of respiratory muscle endurance training.

Introduction

In able bodied subjects the respiratory system was generally accepted as a non exercise limiting factor, as maximal voluntary ventilation is never reached during exercise (11, 26). Nevertheless, fatigued respiratory muscles prior to maximal running exercise reduced performance and oxygen uptake compared to the same test without prior respiratory muscle exercise (23). If fatigued respiratory muscles can limit exercise performance, respiratory training should compensate this effect. In fact, four weeks of respiratory muscle endurance training during 30 min, 5 times a week increased respiratory muscle endurance more than 450% and leg cycling exercise time at the anaerobic threshold by 38% in trained able bodied subjects (6).

Effects of respiratory muscle endurance training on upper body exercise performance have not yet been evaluated. Upper extremity exercise has been shown to change ventilatory muscle recruitment and breathing pattern compared to leg exercise (8, 9). This change decreased physical exercise endurance performance due to the concurrent work of upper body muscles for breathing and exercising (8). Wheelchair racing athletes, using only muscles of the upper extremities seem to be an ideal group to study the effects of respiratory muscle endurance training on upper body endurance exercise performance. Additionally, a spinal cord injury (SCI) causes lesion dependent functional loss of respiratory muscles (13, 25). Subjects with paraplegia mainly miss the abdominal muscles which are important for a forced expiration needed during physical activity (32). The lower total amount of active respiratory muscle mass in subjects with SCI leads, among other effects, to an impairment of respiratory muscle endurance (28) which may additionally affect the disability in physical endurance exercise performance. Therefore, we investigated respiratory muscle endurance training in wheelchair racing athletes. We hypothesize that respiratory muscle endurance training can improve ventilatory muscle endurance and upper body exercise performance on a 10 km time-trial in athletes with paraplegia.

Methods

Subjects

Inclusion criteria were wheelchair dependency, regular training and experience in wheelchair racing competitions. Exclusion criteria were tetraplegia and irregular medication. Twelve competitive wheelchair racing athletes met the above mentioned criteria and participated in the study. A training group (T) and a control group (C) of 6 athletes each were built. Subjects were divided by matched-pairs concerning lesion level. Race classification was considered as well in order to build 2 comparable groups. Subjects' characteristics for T and C including anthropometric and training data are presented in Table 1.

The study was approved by the local ethics committee and written informed consent has been given by each subject prior to the start of the study. Subjects were asked to abstain from caffeine intake on all test days (30). Test preparation (e.g. sleep, nutrition and training during the last 24 h prior to each test) was reported and kept constant within subjects. Subjects were asked for identical test preparation and to perform no strenuous workouts the day before a test. Personal training schedule during the test- and training-phase was kept constant, recorded by each athlete and controlled to be kept constant. The whole study was performed during the winter months when wheelchair racing athletes mainly perform aerobic workout sessions.

Study design

Initially, all subjects reported to the laboratory on 4 separate occasions for baseline testing. All sessions were at least 48 h apart. Baseline testing included lung function measurements, a VO_{2peak} test, a 10 km time-trial and a respiratory muscle endurance test by means of normocapnic hyperpnoea (for descriptions of each test see below). Thereafter, T-subjects performed respiratory muscle endurance training by means of normocapnic hyperpnoea for 6 weeks, while C-subjects did no respiratory muscle training (for detailed description of respiratory muscle endurance training see below). Otherwise, both groups followed their usual wheelchair training during the whole study. After 6 weeks, the 4 baseline testing sessions were repeated in the same order, except familiarization trials. About 3 to 5 days lay in between the last respiratory muscle endurance training and the first test after the training session, to allow respiratory muscles to sufficiently recover from respiratory muscle endurance training (6).

Lung function measurement

Session one included lung function and respiratory muscle strength measurements according to the standards of the ATS (2) by bodyplethysmography (MasterScreen Body, Jaeger, Hoechberg, Germany). Total lung capacity (TLC), residual volume (RV), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), the ratio between FEV_1 and FVC, peak expiratory flow (PEF) maximal voluntary ventilation during 12 s (MVV) were measured. Maximal inspiratory muscle pressure (Pi_{max}) was measured from RV and maximal expiratory muscle pressure (Pe_{max}) was measured from TLC. A small air leak in the measurement device prevented from glottis closure. The whole system was calibrated immediately before each test. The measurement device calculated percent of reference values (1) for FVC, TLC, RV, PEF, FEV_1 and MVV. For calculation of percent predicted of respiratory muscle pressure measurements (Pi_{max} and Pe_{max}), the reference values of Black and Hyatt (5) were used. After lung function measurement, an instruction and familiarization

trial with the respiratory muscle endurance training device (SpiroTiger medical, Idiag AG, Fehraltorf, Switzerland) completed the first session.

VO_{2peak} test

During the second testing session, a VO_{2peak} test was performed in the athlete's own racing wheelchair, which was fixed to a treadmill (Saturn HP Cosmos, Munich, Germany) with a mobile lever arm. Tires of the wheelchairs were pumped to a pressure of 1000 kPa before the test. This test started at a speed of 10 km/h and an inclination of 0.7%. Every 3 min, speed increased for 2 km/h until volitional exhaustion. Oxygen uptake (VO_2), carbon dioxide production (VCO_2), minute ventilation (V_E), respiratory frequency (fR) and tidal volume (V_T) were measured breath-by-breath and averaged over 15 s by an ergospirometer (Oxycon alpha, Jaeger, Hoechberg, Germany). Values were measured using a turbine for volume measurements and fast-responding gas analyzers (O_2 paramagnetic, CO_2 infrared). The system was calibrated with a 3 l syringe and certified mixed calibration gas immediately before each test. VO_{2peak} was determined from the highest VO_2 average of a 15 s period. Heart rate was measured continuously (Polar heart rate monitor, POLAR S610i, Kempele, Finland) and maximal heart rate was analyzed using the corresponding analyzing software of the heart rate monitor (Polar Precision Performance SW, Version 4.00.020, Kempele, Finland). Blood samples (20 µL) were collected from the earlobe before, at the end of the test and 2 min after test break off. Lactate concentrations were analyzed enzymatically (Super GL Ambulance, Ruhrtal Labor Technik, Moehnesee, Germany). Athletes were asked to indicate their individual dyspnoea, perceived respiratory exertion and perceived physical exertion immediately after test break off by means of a visual analogue scale (21). After the VO_{2peak} test, subjects completed a second familiarization trial with the respiratory muscle endurance training device.

10 km time-trial

On the third test session athletes had to complete a 10 km time-trial which was performed in the athlete's own racing chair on a nearly frictionless training roller (Spinner, New Hall's Wheels, Cambridge, USA). Tires of the wheelchairs were pumped to a pressure of 1000 kPa before the test. After a standardized warm-up of 2 km at an intensity of 55-60% of the maximal speed during the VO_{2peak} test, they had to complete 10 km as fast as possible. VO_2, VCO_2, V_E, fR, V_T, end tidal pressure for CO_2 ($PetCO_2$), heart rate, lactate, degree of dyspnoea, perceived respiratory exertion and perceived physical exertion were measured in analogy to the VO_{2peak} test. Mean values of the whole 10 km time-trial for VO_2, V_E, fR, V_T and $PetCO_2$ were calculated from all 15 s average values during the test. Mean VO_2 during the 10 km time-trial was calculated and presented as % of VO_{2peak}. Mean heart rate of the

time-trial was calculated by the heart rate analyzing software tool (Polar Precision Performance SW, Version 4.00.020, Kempele, Finland). No information about velocity, heart rate or exercise time was given to the athletes during the test, except for notification of each accomplished km. After a rest of 20 min, subjects completed a third familiarization trial with the respiratory muscle endurance training device.

Respiratory muscle endurance test

On the fourth session, subjects had to perform a respiratory muscle endurance test with the respiratory muscle endurance training device (SpiroTiger, idiag AG, Fehraltorf, Switzerland). Instrument adjustment as described below was made during the familiarization trials after the lung function test, the VO_{2peak} test and the 10 km time-trial. Target fR and V_T are paced by visual feedback on the respiratory muscle endurance training device. Feedback is given on a hand-held monitor while subjects perform partial rebreathing, breathing in and out of a bag in order to aim for normocapnic conditions. The size of the bag was adjusted to about 50% of the subject's FVC (22). Breathing frequency was adjusted to reach a target V_E which could be maintained for 5 to 10 min during pre-tests, corresponding to an intensity of 65-75% of the individual MVV value. Respiratory muscle endurance training levels around these intensities have been shown to significantly increase respiratory muscle endurance and physical exercise performance in trained able bodied subjects (6, 29). During the respiratory muscle endurance tests, an ergospirometer (Oxycon alpha, Jaeger, Hoechberg, Germany) was used to measure and monitor $PetCO_2$, V_E, fR and V_T breath-by-breath using a metabolic chart. The system was calibrated with a 3 l syringe and certified mixed calibration gas immediately before each test. Heart rate, dyspnoea, perceived respiratory exertion and perceived physical exertion were measured in analogy to the VO_{2peak} test. Blood samples for lactate analysis were taken before, every 2 min during the respiratory muscle endurance test and at test break off. Sample size, analyzing and calibration details were the same as in the other tests described above. The test was stopped either by the experimenter if target V_E could no longer be maintained or by the athlete due to exhaustion. After 6 weeks of respiratory muscle endurance training (T) or no respiratory muscle training (C), respiratory muscle endurance tests were performed at the same target V_E as at baseline testing. If athletes reached 60 min, the tests were stopped by the experimenter.

Respiratory muscle endurance training

Each subject of T conducted 30 training sessions of 30 min each (5 sessions per week, during 6 subsequent weeks). Respiratory muscle endurance training was performed at an intensity which could be maintained for 30 min but not longer; therefore V_E was adapted after baseline testing and increased individually during the training process in order to reach an exhausting

training intensity. One of the 5 training sessions per week was performed in the laboratory to control and adjust training intensity in order to reach the maximal possible training effect. Training time and volume of respiratory muscle endurance training sessions performed at home were saved by the respiratory endurance training device and controlled after the weekly training sessions in the laboratory.

Statistical analysis

Results are presented as mean ± standard deviation (SD). Wilcoxon's rank-sum tests were used to evaluate within groups differences between pre- and post-intervention values for all measured data. Additionally, between groups differences for baseline testing as well as changes from pre- to post-intervention were calculated using Mann-Whitney-U tests. Significance was tested with an alpha level of $p < 0.05$. Statistical analyses were performed with a computer software package (Version 10.2; Systat Software, Inc.; Point Richmond CA, USA).

Results

Baseline data

Anthropometric and wheelchair exercise training data showed no significant differences between T and C (Table 1). Baseline testing showed no significant differences in all measured values between T and C for the respiratory muscle endurance test and the VO_{2peak} test. Baseline values of the 10 km time-trial were significantly different between T and C for respiratory equivalent for O_2 only ($p = 0.04$). Baseline lung function measurements showed significant higher TLC ($p = 0.015$) and a significant lower FEV_1/FVC ratio ($p = 0.026$) and PEF ($p = 0.030$) for T compared to C.

Table 1: Anthropometric and training data of the training (T) and the control group (C)

Group	**sex**	**height** [m]	**weight** [kg]	**age** [y]	**lesion level / ASIA**	**race class**	**lesion since** [y]	**training** [h/week]	**training since** [y]
T	m	1.78	60	46	T4 / B	T53	26	14	24
T	w	1.50	40	34	T6 / A	T52	24	5	12
T	m	1.88	67	29	T6 / A	T53	1.5	5	1
T	w	1.70	46	18	L1 / C	T54	4	6	2
T	m	1.65	50	31	L1 / C	T54	10	7.5	7
T	m	1.73	60	18	L3 / C	T54	18	8.5	6
mean ± SD		**1.70 ± 0.13**	**54 ± 10**	**29 ± 10**			**14 ± 10**	**7.5 ± 3.6**	**9 ± 9**
C	m	1.73	60	40	T5 / A	T53	18	8.5	16
C	m	1.65	65	40	T6 / A	T53	13	8	10
C	m	1.70	58	19	T8 / C	T53	9	6	3
C	w	1.65	50	20	T12/B	T54	11	6	5
C	m	1.68	69	24	L1 / C	T54	24	2.5	8
C	m	1.55	57	27	L3 / C	T54	27	6.5	13
mean ± SD		**1.66 ± 0.06**	**60 ± 7**	**28 ± 10**			**17 ± 7**	**6.3 ± 2.1**	**9 ± 5**

m = man; w = woman; L = lumbar lesion; T = thoracic lesion; ASIA = American Spinal Injury Association; y = years; SD = standard deviation; Note that there were no significant differences between groups.

Respiratory muscle endurance training data

Compliance of the respiratory muscle endurance training was excellent being 100%. T-subjects performed respiratory muscle endurance training at a mean intensity of 64 ± 14% of their individual MVV level during the first week and at 73 ± 16% of MVV during the last week of respiratory muscle endurance training. V_E increased from 80.4 ± 25.6 l/min during the first week to 92.6 ± 32.3 l/min during the last week of respiratory muscle endurance training.

Pre- vs. post-tests data

Respiratory muscle endurance

Respiratory muscle endurance increased significantly by 332% in T ($p = 0.028$) after respiratory muscle endurance training, while C showed a non-significant increase of 53%. A significant difference in effect existed between groups ($p = 0.016$) (Table 2). The break-off level for respiratory muscle endurance tests at 60 min was reached by 2 subjects of T in the post-intervention trial. Thus, these tests were stopped before exhaustion.

Table 2: Mean ± standard deviation of values during respiratory muscle endurance tests

	Training group [n = 6]		**Control group** [n = 6]	
	Pre	**Post**	**Pre**	**Post**
Time of respiratory muscle endurance tests [min]	9.1 ± 7.2	39.9 ± 17.8° †	4.3 ± 2.9	6.6 ± 7.0
Mean heart rate [bpm]	124 ± 13	122 ± 11	130 ± 17	128 ± 19
Mean V_E [l/min]	91 ± 28	91 ± 28	107 ± 18	107 ± 17
Mean tidal volume [l]	2.52 ± 0.90	2.58 ± 0.90	2.82 ± 0.63	2.83 ± 0.60
Mean breathing frequency [min^{-1}]	37 ± 4	35.7 ± 4.8	38 ± 3	38 ± 3
Mean end tidal CO_2 [kPa]	3.9 ± 0.7	3.7 ± 1.3	3.2 ± 1.0	3.4 ± 1.0
Dyspnoea$_{end}$ [VAS]	3.7 ± 3.7	4.6 ± 3.9	5.8 ± 2.5	4.8 ± 4.4
Perceived resp. exertion$_{end}$ [VAS]	8.1 ± 1.4	9.5 ± 0.8	6.5 ± 2.5	6.2 ± 3.1
Perceived phys. exertion$_{end}$ [VAS]	5.7 ± 2.7	7.1 ± 2.9	7.1 ± 1.6	5.0 ± 3.9
Lactate$_{rest}$ [mmol/l]	1.3 ± 0.7	1.3 ± 0.5	1.2 ± 0.6	0.9 ± 0.2
Lactate$_{mean}$ [mmol/l]	1.8 ± 0.7	1.6 ± 0.7	1.8 ± 0.6	1.5 ± 0.6
Lactate$_{end}$ [mmol/l]	1.9 ± 0.8	1.3 ± 0.6	1.9 ± 0.5	1.5 ± 0.8

V_E = minute ventilation; VAS = visual analogue scale [points]; Note that 'Mean' values are means over the whole test duration; ° Significant between groups difference (change between pre- and post- test); † Significant within group difference

Lung function and respiratory muscle strength

There were no significant changes between pre- and post- tests for all measured lung function values as well as for Pi_{max} within and between groups. Pe_{max} increased significantly by 25% within T ($p = 0.028$) but showed no significant differences within C (+ 8%) and nor between groups comparisons (Table 3).

Table 3: Mean ± standard deviation of lung function measurements by bodyplethysmography as % predicted

	Training group [n = 6]		**Control group** [n = 6]	
	Pre	**Post**	**Pre**	**Post**
TLC [%]	89.2 ± 14.9*	90.7 ± 21.8	69.2 ± 8.0	74.3 ± 17.1
RV [%]	171.6 ± 31.0	176.5 ± 35.7	144.1 ± 29.6	138.6 ± 38.0
FVC [%]	85.3 ± 29.0	88.5 ± 31.3	94.6 ± 30.9	95.8 ± 26.0
FEV_1 [%]	84.5 ± 26.6	87.4 ± 28.4	101.7 ± 27.5	103.2 ± 23.1
FEV_1/FVC [%]	102.1 ± 10.8*	102.7 ± 11.2	114.2 ± 10.8	113.6 ± 8.8
PEF [%]	76.8 ± 20.6*	83.3 ± 28.1	104.8 ± 13.3	112.9 ± 19.2
MVV [%]	124.8 ± 61.9	134.4 ± 66.7	118.8 ± 12.6	126.3 ± 15.3
Pi_{max} [%]	90.8 ± 29.3	102.3 ± 17.7	104.2 ± 16.7	104.5 ± 17.7
Pe_{max} [%]	46.4 ± 11.3	59.8 ± 11.2 †	52.4 ± 16.2	56.3 ± 15.4

TLC = total lung capacity, RV = residual volume, FVC = forced vital capacity, FEV_1 = forced expiratory volume in 1 s, PEF = peak expiratory flow, MVV = maximal voluntary ventilation, Pi_{max} = maximal inspiratory muscle pressure, Pe_{max} = maximal expiratory muscle pressure; Note that there were no significant differences in changes from pre- to post-test between groups; * Significant between groups difference (baseline testing); † Significant within group difference

10 km time-trial

10 km time-trial performance showed significant within group differences for T ($p = 0.046$) but not for C (Table 4). Between groups comparisons were not significantly different ($p = 0.150$). Individual results of the 10 km time-trial pre- vs. post-intervention are shown in Figure 1. While 5 of 6 subjects of T decreased exercise time, only 2 subjects of C did so. The effect size of the 10 km time-trial was $d = 0.87$.

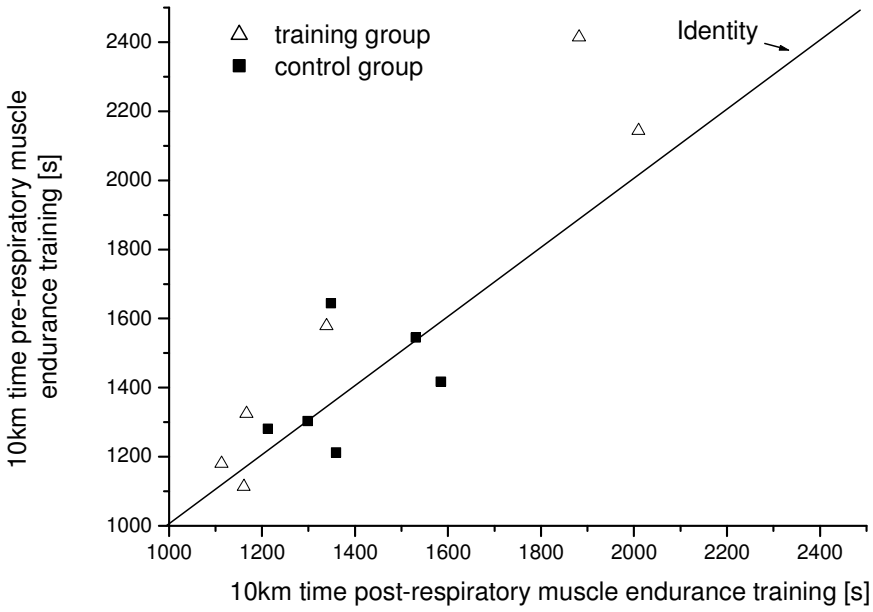


Figure 1: Individual results of the relationship between times of 10 km time-trial pre- (y-axis) vs. post- (x-axis) respiratory muscle endurance training

Mean decrease in 10 km time-trial performance was 11.1% in T, while mean decrease in C was only 0.8%. There was a significant between groups difference in mean V_E ($p = 0.025$) pre- vs. post- intervention, and a significant within T increase in V_T ($p = 0.046$) (Table 4). Mean V_E for all T- and C-subjects during 10 km time-trials were between 40 and 48% of MVV values. Lactate concentrations at the end and 2 min after the end of the 10 km time-trial were significantly different within T ($p = 0.046$) as well as between groups ($p= 0.016$) (Table 4).

Table 4: Mean ± standard deviation of the 10km time-trial data

	Training group [n = 6]		**Control group** [n = 6]	
	Pre	**Post**	**Pre**	**Post**
Time of 10 km time-trial [min]	27.1 ± 9.0	24.1 ± 6.6 †	23.3 ± 2.8	23.2 ± 2.4
Mean VO_2 as % of VO_{2peak}	71.5 ± 9.9	77.1 ± 12.2	77.8 ± 4.6	74.6 ± 7.7
Mean heart rate [bpm]	161 ± 13	168 ± 15	173 ± 11	172 ± 14
Mean V_E [l/min]	52.6 ± 18.6	64.6 ± 27.9 °	75.5 ± 24.3	68.3 ± 19.0
Mean tidal volume [l]	1.28 ± 0.33	1.47 ± 0.51 †	1.43 ± 0.69	1.40 ± 0.56
Respiratory equivalent for O_2	30.6 ± 2.3*	28.5 ± 3.9	24.6 ± 2.0	25.8 ± 3.4
Mean breathing frequency [min^{-1}]	41.5 ± 11.6	44.8 ± 13.2	57.5 ± 17.9	52.5 ± 9.1
Mean end tidal CO_2 [kPa]	3.3 ± 0.2	3.3 ± 0.3	2.9 ± 0.4	3.0 ± 0.2
$Dyspnoea_{end}$ [VAS]	3.5 ± 3.7	4.4 ± 3.5	3.6 ± 3.8	5.1 ± 3.8
Perceived respiratory $exertion_{end}$ [VAS]	6.3 ± 3.4	7.5 ± 3.7	6.3 ± 2.5	6.6 ± 3.2
Perceived physical $exertion_{end}$ [VAS]	7.5 ± 2.3	8.7 ± 2.7	8.8 ± 1.8	8.4 ± 1.9
$Lactate_{rest}$ [mmol/l]	1.2 ± 0.4	1.2 ± 0.6	1.2 ± 0.4	1.0 ± 0.4
$Lactate_{end}$ [mmol/l]	5.7 ± 3.7	7.4 ± 4.4° †	8.7 ± 4.3	7.2 ± 3.5
$Lactate_{2min\ post}$ [mmol/l]	5.9 ± 3.9	7.2 ± 4.4° †	8.1 ± 3.9	6.9 ± 3.3

VO_2 = oxygen uptake; V_E = minute ventilation; VAS = visual analogue scale [points]; * Significant between groups difference (baseline testing); ° Significant between groups difference (change between pre- and post-tests); † Significant within group difference; Note that 'Mean' values are calculated means over the whole 10 km time-trial.

VO_{2peak} test

Peak oxygen consumption as well as all other measured values (shown in Table 5) of the VO_{2peak} test showed no significant differences pre- vs. post-intervention for within as well as between groups comparisons.

Table 5: Mean ± standard deviation of VO_{2peak} test values

	Training group [n = 6]		**Control group** [n = 6]	
	Pre	**Post**	**Pre**	**Post**
VO_{2peak} [ml/min/kg]	41.2 ± 10.6	40.3 ± 6.8	38.4 ± 7.7	37.4 ± 6.9
Heart rate$_{max}$ [bpm]	185 ± 16	184 ± 14	191 ± 7	190 ± 6
V_{Emax} [l/min]	96 ± 31	94 ± 30	109 ± 22	114 ± 25
Tidal volume$_{max}$ [l]	1.97 ± 0.61	1.96 ± 0.56	2.08 ± 0.69	2.03 ± 0.82
Breathing frequency$_{max}$ [min^{-1}]	60 ± 13	62 ± 14	77 ± 20	76 ± 21
Dyspnoea$_{end}$ [VAS]	2.7 ± 2.1	3.6 ± 2.6	2.4 ± 3.1	5.5 ± 3.9
Perceived respiratory exertion$_{end}$ [VAS]	6.1 ± 3.4	7.7 ± 3.0	5.5 ± 3.1	6.7 ± 3.2
Perceived physical exertion$_{end}$ [VAS]	8.3 ± 1.7	8.9 ± 1.2	8.9 ± 1.2	9.0 ± 1.1
Lactate$_{rest}$ [mmol/l]	1.2 ± 0.5	1.2 ± 0.4	1.3 ± 0.1	0.9 ± 0.3
Lactate$_{end}$ [mmol/l]	8.7 ± 3.7	8.3 ± 2.3	9.0 ± 1.8	8.7 ± 2.5
Lactate$_{2minpost}$ [mmol/l]	7.9 ± 3.4	8.0 ± 2.3	8.9 ± 1.3	8.3 ± 2.2

VO_{2peak} = peak oxygen uptake, $V_{E\,max}$ = maximal minute ventilation, VAS = visual analogue scale [points]; Note that there were no significant differences in changes from pre- to post-tests between groups.

Discussion

Summary of major findings

This study showed that respiratory muscle endurance training has a positive effect on respiratory muscle endurance of wheelchair racing athletes, but much less effects on exercise performance. Six weeks of respiratory muscle endurance training significantly increased respiratory muscle endurance in trained athletes with paraplegia. Further, this study provides first evidence that respiratory muscle endurance training may also increase upper extremity exercise performance, showing significant within T decreases in exercise time on a 10 km time-trial (effect size d = 0.87).

Spirometry and respiratory muscle endurance test

Baseline testing of lung function (Table 3) indicates that FVC, FEV_1, FEV_1/FVC, PEF, MVV and Pi_{max} are close to normal and that T may have more potential to improve lung function by respiratory muscle endurance training than C, since FEV_1/FVC and PEF were significantly lower in T than in C. Nevertheless, post lung function results provide evidence that this difference was no confounding factor on outcomes of this study, since neither within nor between groups differences showed any significance for all lung function values pre- vs. post-intervention. The more or less normal lung function values in paraplegic athletes are most likely the result of regular physical exercise training, which may possibly compensate the loss

of some respiratory muscle function (32) leading to nearly normal lung function values. Despite normal lung function in our SCI subjects, Pe_{max} was severely decreased (Table 3). Decreases in Pe_{max} occur due to the loss of abdominal muscle function and lesion dependent intercostal muscle function loss (32). Interestingly, Pe_{max} seems to be positively influenced by respiratory muscle endurance training since it significantly increased within T. Thus, respiratory muscle endurance training may also be an interesting option for sedentary subjects with SCI or during SCI rehabilitation to improve expiratory muscle strength.

Our results show that respiratory muscle endurance training improves respiratory muscle endurance in athletes with paraplegia to a comparable extent as in able bodied individuals (6, 7). Results of C reveal that there was no learning effect between pre- and post-intervention values.

10 km time-trial

T-subjects showed a significant within group difference with a mean decrease in time of 11% over a 10 km time trial, which has a practical relevance for wheelchair racing competitions. Unfortunately, the high inter-individual variability (in combination with the small groups) caused a non-significant between groups difference ($p = 0.150$). Nevertheless, there was a strong trend with a large observed effect size of $d = 0.87$, towards improved performance in the 10 km time-trial after six weeks of respiratory muscle endurance training.

The reproducibility of an exercise test to measure physical performance is an important factor to reduce variability of results. While most of respiratory muscle endurance training studies performed in able bodied subjects were conducted by constant load cycling endurance tests to exhaustion (6, 7), our athletes had to complete a time-trial since reproducibility has been shown to be much higher in time-trials (CV 3.4%) than in sub-maximal endurance exercise tests (CV 26.6%) (14, 15). Additionally, a time-trial is more competition like than a sub-maximal endurance test and therefore more meaningful to competitive athletes. Probably other individual differences as day-to-day variation, lesion level, muscle fibre type distribution or motivational aspects contributed to the inter-individual differences.

This study is the first investigating effects of respiratory muscle endurance training on upper extremity exercise performance. During upper body exercise, similar muscles are innervated for movement and breathing and therefore these muscles are concurrently used. It has been shown that ventilatory pattern change during upper body exercise, and exercise endurance is decreased compared to leg exercise (8). Therefore, improvements in respiratory muscle endurance may have a positive influence on upper body exercise performance. Probably this was only the case in some of the tested athletes of the present study. The lesion dependent differences in the amount of innervated upper body muscle mass differs between athletes and

may therefore provide a source of variation in exercise performance and potential to increase upper body endurance performance.

The difference in ventilatory work during upper body exercise compared to leg exercise is another important factor to be considered. Studies of upper body and/or leg exercise have shown that arm-cranking exercise at maximal effort only needs between 70 to 80% of total V_E needed during maximal leg cycling exercise (4, 10, 27). While T-subjects showed a mean V_E level of 40.4% MVV during the pre- and 46.5% MVV during the post- time-trial, able bodied subjects performed cycling endurance tests at V_E levels between 56 to 64% MVV before respiratory muscle endurance training and were even able to reduce V_E during the test after respiratory muscle endurance training to 39-51% MVV (6, 7, 29). The lower percentage of maximal V_E levels found in wheelchair racing athletes during a 10 km time-trial may fatigue respiratory muscles to a lesser extent than those of able bodied subjects during cycling at a comparable exercise time. Thus, although respiratory muscle endurance increased, respiratory muscle fatigue during the 10 km time-trial may not be the limiting factor in some of our wheelchair racing athletes. Probably a time-trial over 20 km or even the marathon distance would provide more consistent results.

Other studies investigating respiratory muscle endurance training in able bodied subjects found that some of the tested subjects showed a higher V_E during physical exercise testing after respiratory muscle endurance training, compared to the same test before respiratory muscle endurance training (6, 18). Interestingly, endurance exercise time of a constant load test was decreased in these subjects with increased V_E levels, while endurance exercise time of those subjects who had a lower V_E after respiratory muscle endurance training was increased. Results of T in the present study demonstrate a similar pattern since the subject with the highest improvement in the 10 km time-trial performance had a lower mean V_E and the only subject of T who's 10 km time increased showed the highest mean increase in V_E during the time-trial post respiratory muscle endurance training. This finding could occur either due to the hyperpnoea performed for respiratory muscle endurance training which may lead to a higher V_E during physical exercise by conditioning of respiratory regulation which is known to have certain plasticity (17), or due to insufficient recovery time after respiratory muscle endurance training (6). This fact may be a further source of individual variation between subjects.

VO_{2peak}

VO_{2peak} did, as expected, not increase after respiratory muscle endurance training in the present study. Similar results have been reported in many other studies (3, 6, 7, 16, 19, 24, 29). To increase VO_{2peak} it has been shown that training on a very high intensity level is necessary and that one achieves a higher increase in VO_{2peak} due to intermittent exercise rather

than due to endurance exercise training (12, 20, 31). Thus, an increase in VO_{2peak} could not be expected, nor due to respiratory muscle endurance training, and neither due to physical exercise training since subjects hold their wheelchair training constant on an aerobic intensity level.

Limitation

The fact that the results of the 10 km time-trial were not statistically significant between groups is most likely due to large inter-individual differences and small groups. Although the groups were small, they were quite well matched for lesion level.

Clinical relevance

This study reveals that respiratory muscle endurance can be increased in competitive athletes with paraplegia by isolated respiratory muscle endurance training. Our results show preliminary indices which may be interesting for the rehabilitation of patients with spinal cord injury, especially the significant within T increase in Pe_{max}.

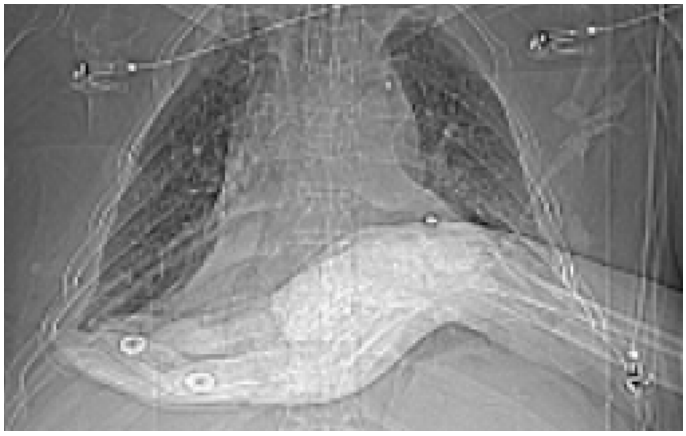
Conclusion

This study showed that six weeks of respiratory muscle endurance training performed by competitive wheelchair racing athletes increased respiratory muscle endurance. Since there was a large observed effect size of d = 0.87, there is evidence that six weeks of respiratory muscle endurance training may also improve upper body exercise performance.

References

1. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. *Am Rev Respir Dis* 144: 1202-1218, 1991.
2. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 152: 1107-1136, 1995.
3. **Belman MJ, and Gaesser GA**. Ventilatory muscle training in the elderly. *J Appl Physiol* 64: 899-905, 1988.
4. **Bergh U, Kanstrup IL, and Ekblom B**. Maximal oxygen uptake during exercise with various combinations of arm and leg work. *J Appl Physiol* 41: 191-196, 1976.
5. **Black LF, and Hyatt RE**. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 99: 696-702, 1969.
6. **Boutellier U, Buchel R, Kundert A, and Spengler C**. The respiratory system as an exercise limiting factor in normal trained subjects. *Eur J Appl Physiol Occup Physiol* 65: 347-353, 1992.
7. **Boutellier U, and Piwko P**. The respiratory system as an exercise limiting factor in normal sedentary subjects. *Eur J Appl Physiol Occup Physiol* 64: 145-152, 1992.
8. **Celli B, Criner G, and Rassulo J**. Ventilatory muscle recruitment during unsupported arm exercise in normal subjects. *J Appl Physiol* 64: 1936-1941, 1988.
9. **Cerny FJ, and Ucer C**. Arm work interferes with normal ventilation. *Appl Ergon* 35: 411-415, 2004.

10. **Davis JA, Vodak P, Wilmore JH, Vodak J, and Kurtz P**. Anaerobic threshold and maximal aerobic power for three modes of exercise. *J Appl Physiol* 41: 544-550, 1976.
11. **Dempsey JA**. J.B. Wolffe memorial lecture. Is the lung built for exercise? *Med Sci Sports Exerc*18: 143-155, 1986.
12. **Gimenez M, Cereceda V, Teculescu D, Aug F, and Laxenaire MC**. Square-wave endurance exercise test (SWEET) for training and assessment in trained and untrained subjects. III. Effect on VO2 max and maximal ventilation. *Eur J Appl Physiol Occup Physiol* 49: 379-387, 1982.
13. **Haas A, Lowman EW, and Bergofsky EH**. Impairment of Respiration after Spinal Cord Injury. *Arch Phys Med Rehabil* 46: 399-405, 1965.
14. **Holm P, Sattler A, and Fregosi RF**. Endurance training of respiratory muscles improves cycling performance in fit young cyclists. *BMC Physiol* 4: 9, 2004.
15. **Jeukendrup A, Saris WH, Brouns F, and Kester AD**. A new validated endurance performance test. *Med Sci Sports Exerc* 28: 266-270, 1996.
16. **Keens TG, Krastins IR, Wannamaker EM, Levison H, Crozier DN, and Bryan AC**. Ventilatory muscle endurance training in normal subjects and patients with cystic fibrosis. *Am Rev Respir Dis* 116: 853-860, 1977.
17. **Kinkead R, Bach KB, Johnson SM, Hodgeman BA, and Mitchell GS**. Plasticity in respiratory motor control: intermittent hypoxia and hypercapnia activate opposing serotonergic and noradrenergic modulatory systems. *Comp Biochem Physiol A Mol Integr Physiol* 130: 207-218, 2001.
18. **Kohl J, Koller EA, Brandenberger M, Cardenas M, and Boutellier U**. Effect of exercise-induced hyperventilation on airway resistance and cycling endurance. *EurJ Appl Physiol Occup Physiol* 75: 305-311, 1997.
19. **Leith DE, and Bradley M**. Ventilatory muscle strength and endurance training. *J Appl Physiol* 41: 508-516, 1976.
20. **MacDougall JD, Hicks AL, MacDonald JR, McKelvie RS, Green HJ, and Smith KM**. Muscle performance and enzymatic adaptations to sprint interval training. *J Appl Physiol* 84: 2138-2142, 1998.
21. **Mador MJ, and Kufel TJ**. Reproducibility of visual analog scale measurements of dyspnea in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 146: 82-87, 1992.
22. **Markov G, Spengler CM, Knopfli-Lenzin C, Stuessi C, and Boutellier U**. Respiratory muscle training increases cycling endurance without affecting cardiovascular responses to exercise. *Eur J Appl Physiol* 85: 233-239, 2001.
23. **Martin BJ, and Stager JM**. Ventilatory endurance in athletes and non-athletes. *Med Sci Sports Exerc* 13: 21-26, 1981.
24. **Morgan DW, Kohrt WM, Bates BJ, and Skinner JS**. Effects of respiratory muscle endurance training on ventilatory and endurance performance of moderately trained cyclists. *Int J Sports Med* 8: 88-93, 1987.
25. **Ohry A, Molho M, and Rozin R**. Alterations of pulmonary function in spinal cord injured patients. *Paraplegia* 13: 101-108, 1975.
26. **Ouellet Y, Poh SC, and Becklake MR**. Circulatory factors limiting maximal aerobic exercise capacity. *J Appl Physiol* 27: 874-880, 1969.
27. **Sawka MN, Miles DS, Petrofsky JS, and Glaser RM**. Arterial carbon dioxide estimates during upper body exercise. *Eur J Appl Physiol Occup Physiol* 48: 415-422, 1982.
28. **Silva AC, Neder JA, Chiurciu MV, Pasqualin DC, da Silva RC, Fernadez AC, Lauro FA, de Mello MT, and Tufik S**. Effect of aerobic training on ventilatory muscle endurance of spinal cord injured men. *Spinal Cord* 36: 240-245, 1998.
29. **Spengler CM, Roos M, Laube SM, and Boutellier U**. Decreased exercice blood lactate concentrations after respiratory endurance training in humans. *EurJ Appl Physiol Occup Physiol* 79: 299-305, 1999.
30. **Supinski GS, Levin S, and Kelsen SG**. Caffeine effect on respiratory muscle endurance and sense of effort during loaded breathing. *J Appl Physiol* 60: 2040-2047, 1986.
31. **Tabata I, Nishimura K, Kouzaki M, Hirai Y, Ogita F, Miyachi M, and Yamamoto K**. Effects of moderate-intensity endurance and high-intensity intermittent training on anaerobic capacity and VO2max. *Med Sci Sports Exerc* 28: 1327-1330, 1996.
32. **Winslow C, and Rozovsky J**. Effect of spinal cord injury on the respiratory system. *Am J Phys Med Rehabil / Assoc Acad Physiatr* 82: 803-814, 2003.



Chapter 6

Impact of Low Intensity Isocapnic Hyperpnoea on Blood Lactate Disappearance after Exhaustive Arm Exercise

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Abstract

Objective: To investigate the impact of low intensity isocapnic hyperpnoea on blood lactate disappearance after exhaustive arm exercise in comparison to passive and active recovery using the previously loaded muscle group.

Methods: Eighteen healthy, non-smoking and physically active male subjects participated in this randomized crossover trial. Subjects performed three arm cranking tests to volitional exhaustion on 3 different days at least 48 h apart. Arm exercise was randomly followed by 30 min of passive recovery, active arm cranking at 30% of peak power output or ventilatory recovery by means of isocapnic hyperpnoea at 30% of their individual maximal voluntary ventilation. Blood lactate concentrations were measured every 2 min during recovery. Blood lactate disappearance during the three different recovery strategies was the main outcome measure of this study.

Results: No significant differences for blood lactate concentrations were found between the three interventions passive recovery, arm cranking and ventilatory recovery during the whole measurement period. Peak lactate concentrations were 11.09 ± 1.98 $mmol \cdot l^{-1}$ for passive recovery, 11.13 ± 1.44 $mmol \cdot l^{-1}$ for arm cranking and 11.25 ± 1.93 $mmol \cdot l^{-1}$ for ventilatory recovery. At the end of the recovery period measured lactate concentrations were 4.35 ± 1.56 $mmol \cdot l^{-1}$ for passive recovery, 3.77 ± 1.60 $mmol \cdot l^{-1}$ for arm cranking and 4.09 ± 1.35 $mmol \cdot l^{-1}$ for ventilatory recovery. Moreover, all other parameters measured were not significantly different, with the exception of higher average recovery heart rates during arm cranking (116 ± 9 bpm) and ventilatory recovery (111 ± 7 bpm) compared to passive recovery (93 ± 11 bpm).

Conclusion: Low intensity isocapnic hyperpnoea seems not to enhance blood lactate disappearance after exhaustive arm exercise compared to passive or active recovery using the previously loaded muscle group. The magnitude of the involved muscle mass appears critical to effective active recovery.

Introduction

Exhaustive anaerobic exercise leads to a large production of lactate and hydrogen ions in the exercising muscles causing a concomitant decrease in intracellular pH (3, 16). This acidosis impairs the ability for muscle contraction and glycolytic enzyme activity leading to reduced exercise performance (16). In order to regain optimal performance as soon as possible, fast lactic acid elimination is crucial for athletes, particularly if there are repeated, high intensity bouts of exercise within a short period of time such as competitions in swimming, athletics or wheelchair racing (24, 25).

In general, blood lactate elimination is accelerated by active recovery of the previously loaded muscle group at moderate intensities (1, 5, 14, 15, 25, 30, 33). In practice, due to restricted infrastructural possibilities or a densely packed schedule during a competition, active recovery is not always possible. Moreover, active recovery using the previously loaded muscle group may impair subsequent exercise performance as energy stores become additionally depleted (11), early resynthesis of muscle glycogen is compromised, and time for an optimal refilling of glycogen stores is shortened (9). This might have negative consequences for subsequent exercise performance, especially in sports or situations where it is not possible to use another muscle group for active recovery purposes (e.g. leg exercise after upper body exercise) as is the case in spinal cord injured athletes.

Type I fibres are able to metabolize lactate (7, 18, 23). As respiratory muscles mainly consist of type I fibres (17, 19, 26), we hypothesized that respiratory muscles may have the potential to enhance blood lactate elimination. If this is the case, respiratory muscles might be used as an easy to handle tool to accelerate blood lactate elimination without affecting glycogen resynthesis in previously exhausted limb muscles. The aim of the present study was to investigate the impact of low intensity isocapnic hyperpnoea on blood lactate disappearance after exhaustive arm exercise and to compare these data with results of conventional active and passive recovery protocols. An acceleration of blood lactate elimination by active recovery strategies (moderate arm cranking exercise and isocapnic hyperpnoea) was expected compared to that of passive recovery.

Methods

Subjects

Eighteen trained, male and non-smoking subjects participated in this study. Their average age was 30 ± 5 years, height 178 ± 7 cm, weight 72 ± 9 kg, weekly physical training volume 5.6 ± 3.3 h and peak oxygen uptake (VO_{2peak}) for arm cranking 42 ± 7 $ml \cdot min^{-1} \cdot kg^{-1}$. Subjects were asked not to perform any strenuous exercise and eat food rich in carbohydrates the day before testing as well as to abstain from caffeine intake on the test days. The study was approved by

the local ethics committee. Written informed consent of the subjects was obtained prior to the start of the study.

Experimental Procedure

Two preliminary sessions preceded the three main test trials. During the first preliminary session, standard spirometric data, including forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), peak expiratory flow rate (PEF) and maximal voluntary ventilation over 12 s (MVV) were obtained by an ergospirometric device (Oxycon Alpha, Jaeger, Hoechberg, Germany). Afterwards, a familiarization trial for isocapnic hyperpnoea by partial rebreathing from a bag was completed (SpiroTiger, idiag AG, Fehraltorf, Switzerland). Bag size corresponded to about one third of subjects' FVC. Subjects were breathing at a preset respiratory frequency to reach target minute ventilation (see below).

The second preliminary session consisted of 30 min continuous isocapnic hyperpnoea at a minute ventilation corresponding to 30% MVV and served to make sure that subjects were able to sustain this load over 30 min. To assure the predetermined target ventilation, tidal volume, breathing frequency and end tidal partial pressure for carbon dioxide were monitored by means of the above mentioned metabolic cart. If necessary, subjects were guided to keep preset tidal volume and breathing frequency to achieve the target ventilation.

All three main tests started with a 2 min resting period for baseline data determination. Subjects were seated in a chair connected to an arm cranking ergometer (Ergometrics 800 SH, Ergoline, Bitz, Germany). After this resting period subjects started arm cranking at 20 W. Then, the workload was increased by 5 W every 20 s until subjects' volitional exhaustion. Respiratory variables at rest and during the exercise tests were sampled breath by breath via a face mask by an Oxycon Pro (Jaeger, Würzburg, Germany). This device was calibrated for gas and volume according to the manufacturers' recommendations immediately before each test. The three main tests were at least 48 h apart.

During arm cranking, the pedal axis of the ergometer was aligned with the shoulder joint axis and subjects were positioned such that the elbow was slightly flexed at maximal reach. Five minutes after test cessation, subjects followed one of three recovery strategies in a randomized order. These strategies were passive recovery, active recovery by arm cranking or ventilatory recovery by means of isocapnic hyperpnoea for 30 min. Whilst subjects sat relaxed on a chair for passive recovery, they were either arm cranking at 30% of the previously reached maximal workload (arm cranking) or breathing at 30% MVV with the SpiroTiger device (ventilatory recovery) as an active recovery strategy.

Capillary blood for enzymatic lactate analysis (Super GL Ambulance, Ruhrtal Labor Technik, Möhnesee, Germany) was sampled from an earlobe at rest, immediately after cessation of the exercise test and every 2 min until the end of the recovery phase. Heart rate was determined

by a heart rate monitor (Polar S610, Polar, Kempele, Finland) throughout the whole test and recovery period. Immediately after cessation of the arm cranking exercise test, subjects were asked to rate their perceived exertion by means of a Borg scale, with 6 indicating 'no' and 20 'maximal' exhaustion (6).

Statistics

Data points of the measured lactate concentrations of the three different recovery strategies were fitted to the following bi-exponential curve, as described in detail elsewhere (13):

$$La(t) = La(0) + A_1 \cdot (1 - e^{-\gamma_1 \cdot t}) + A_2 \cdot (1 - e^{-\gamma_2 \cdot t})$$

La(t) denotes the time dependent lactate concentration with La(0) being the lactate concentration at the start of recovery. The form of this equation suggests that the lactate kinetics during recovery can be described by two main processes, one with a high-velocity constant (γ_1) describing the appearance ($A_1 > 0$) of lactate in the bloodstream and the other with a low-velocity constant (γ_2) describing its disappearance ($A_2 < 0$).

The parameters were calculated using a commercially available computer software package (SYSTAT, Version 10, SPSS Inc., Richmond, California) with the regression method of least mean squares.

An analysis of variance for repeated measures was applied to compare γ_1 as well as γ_2 between the different intervention strategies (passive recovery, arm cranking, ventilatory recovery). In addition, VO_{2peak}, peak power, rating of perceived exertion as well as maximal and average recovery heart rates were analyzed in the same way. If significance was found, a post-hoc test with Bonferroni correction was used to locate significant differences. Results are given as mean ± SD. Values were considered to be significantly different if $p < 0.05$.

Ventilatory threshold of the exercise test preceding arm cranking was calculated from carbon dioxide output (VCO_2) and VO_2 values according to the V-slope method (4).

Results

The mean of the subjects' FVC was 5.8 ± 1.1 l (115% predicted), FEV_1 4.6 ± 0.7 l (109% predicted), PEF 11.4 ± 1.4 $l \cdot s^{-1}$ (119% predicted) and MVV 207 ± 30 $l \cdot min^{-1}$ (140% predicted). Peak power output, VO_{2peak}, maximal heart rate and rating of perceived exertion did not differ significantly between tests (Table 1).

Table 1: Values measured (mean ± standard deviation) at the end of exhaustive arm cranking tests before starting different recovery strategies.

	Subsequent recovery strategy:		
	passive	**arm cranking**	**isocapnic hyperpnoea**
Peak power [W]	148 ± 25	148 ± 23	147 ± 23
Peak oxygen uptake [ml·min^{-1}·kg^{-1}]	41.7 ± 7.3	40.6 ± 4.8	41.7 ± 8.0
Maximal heart rate [bpm]	176 ± 12	176 ± 10	176 ± 11
Rate of perceived exertion (Borg)	18.3 ± 1.4	18.3 ± 1.4	18.2 ± 1.2

Note that there were no significant differences between tests

Blood lactate curves are shown in Figure 1. The low-velocity constants (γ_2) describing blood lactate disappearance were 0.052 ± 0.031 min^{-1} for passive recovery, 0.072 ± 0.035 min^{-1} for arm cranking and 0.053 ± 0.032 min^{-1} for ventilatory recovery ($p = 0.138$) indicating that blood lactate elimination rate constants after exhaustive arm ergometry were not significantly different among the three different recovery strategies. Average recovery heart rates during arm cranking (116 ± 9 bpm) and ventilatory recovery (111 ± 9 bpm) were significantly higher compared to average heart rate during passive recovery (93 ± 11 bpm).

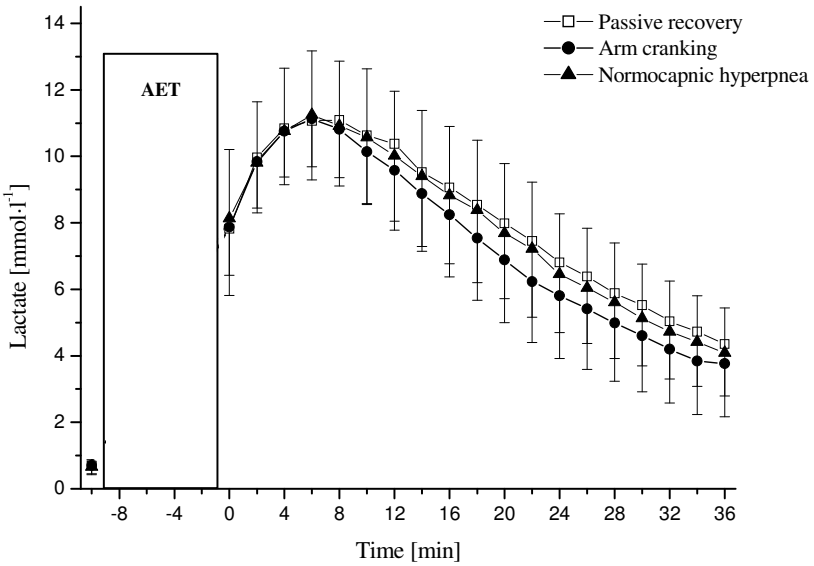


Figure 1: Mean blood lactate elimination curves for differrent recovery strategies after an exhaustive arm cranking exercise test (AET).

Average workload during arm cranking was 44.2 ± 7.3 W corresponding to 29.9 ± 1.0% of peak power output. This workload was clearly below the ventilatory threshold at 55.8 ± 14.5% of VO_{2peak}, which corresponded to an absolute workload of 88.1 ± 30.0 W.

During ventilatory recovery subjects were ventilating 61.6 ± 9.3 $l \cdot min^{-1}$ (29.8 ± 0.9% of MVV) at an average breathing frequency of 26.2 ± 3.7 min^{-1}. Average end tidal partial pressure for carbon dioxide was 32.8 ± 5.1 mmHg.

Discussion

The main finding of this study is that there were no significant differences in blood lactate disappearance after exhaustive arm cranking exercise due to the different recovery strategies. This was surprising, as a superior impact of active recovery strategies (arm cranking and ventilatory recovery) on blood lactate elimination was expected compared to passive recovery. Different reasons may explain this observation and are discussed below.

Arm cranking for active recovery

Active recovery at moderate intensities by means of the previously loaded muscle groups is known to accelerate blood lactate elimination compared to passive recovery (1, 5, 14, 15, 25, 30, 33). Although arm cranking showed a nearly 40% faster low-velocity constant (γ_2) compared to passive recovery and ventilatory recovery, no statistically significant differences ($p = 0.138$) were found between the different recovery strategies. This might be due to relatively large inter-individual differences between subjects (Figure 1) but may also have other reasons which are discussed below.

In contrast to the above mentioned studies where leg exercise was applied, we used arm cranking exercise for recovery. Slower blood lactate kinetics for arm exercise compared to leg exercise were also reported by Thiriet et al. (32). Obviously, the magnitude of the involved muscle mass appears to be critical to an effective active recovery. In fact, arm muscle mass in a group of 29 years old men was found to be only 40% of leg muscle mass (7.1 kg vs. 17.7 kg) (27). Taking further into account the higher proportion of type I fibres (17, 31) combined with the bigger muscle mass involved during leg exercise, it seems not to be surprising that results are different for leg muscles as opposed to arm muscles with regard to lactate elimination. The large proportion of type II fibres in arm muscles (17, 31) limits the capacity to oxidize lactate per se. In combination with the relatively small muscle mass of the arms, lactate elimination is additionally compromised compared to leg muscles.

If the chosen intensity for arm cranking had been too high, lactate elimination would have been decelerated. However, considering the measured mean recovery heart rate of 116 bpm during arm cranking (Table 1) compared to other active recovery heart rates reported in the

literature (14, 25, 32), it seems very unlikely that our recovery intensity of 30% of maximal power output was too high. Moreover, a recovery load of 30% of maximal power output was suggested to be within the optimal range for active recovery and was successfully applied in the past (10, 22, 32). Further, the chosen recovery workload was far below the ventilatory threshold, which supports the assumption of an optimal active recovery intensity.

However, the present active recovery design by means of arm cranking (instead of using previously unloaded leg muscles) was chosen, since there are situations, where it is not possible to use another muscle group for active recovery purposes as it is the case e.g. in spinal cord injured athletes.

Ventilatory recovery for active recovery

With regard to the muscle fibre type composition of arm vs. respiratory muscles, one can hypothesize that ventilatory recovery is superior to arm cranking and passive recovery in accelerating blood lactate disappearance. However, this assumption was not supported by the present findings. Although respiratory muscles mainly contain type I fibres (17, 19, 26), the total muscle mass involved in ventilation is quite small and thus oxidative capacity is limited. Diaphragmatic muscle mass was found to be only 262 g (2) compared to the above mentioned 7 kg of arm muscle mass (27). Even if the auxiliary respiratory muscles worked actively during ventilatory recovery, it seems to be a very small active muscle mass to engage in lactate oxidation. This might be the main reason why the ventilatory recovery strategy failed to enhance blood lactate elimination.

A further reason might be, that the chosen intensity of isocapnic hyperpnoea at 30% MVV was too low to cause a sufficient effect on lactate metabolisation over 30 min. On the other hand, a higher intensity of isocapnic hyperpnoea may have led to respiratory muscle fatigue, which compromises subsequent exercise performance (20, 21). Martin and coworkers (21) showed that intense isocapnic hyperpnoea at 66% of the mean MVV reduces subsequent running performance. It has to be taken into account that during upper body exercise, some of the respiratory muscles of the rib cage have to partake in nonventilatory functions (8). Thus, a recovery strategy like isocapnic hyperpnoea integrating all respiratory muscles should be performed at a moderate intensity, to avoid the development of rib cage muscle fatigue, which otherwise might compromise subsequent arm cranking performance. The fact that average recovery heart rate during ventilatory recovery was close to the heart rate values during arm cranking and significantly higher than during passive recovery underlines that the chosen intensity of isocapnic hyperpnoea at 30% MVV seems to be adequate and comparable to the intensity during arm cranking. Hence, it is questionable if a higher intensity of isocapnic hyperpnoea (e.g. 40-50% MVV) would provide faster lactate removal without causing respiratory muscle fatigue.

Perhaps specifically trained respiratory muscles would have provided faster blood lactate elimination. This assumption is supported by the finding of Spengler et al. (29), who demonstrated lower blood lactate concentrations at the end of exhaustive cycling exercise after 4 weeks of isocapnic hyperpnoea training. It was suggested by the authors that the decrease in blood lactate concentration was most likely caused by an enhanced lactate uptake of the trained respiratory muscles. In contrast, others observed no changes of blood lactate concentrations after respiratory muscle training (28). As the respiratory muscles of our subjects were not specifically trained, it may be interesting to see if there would be differences in the potential for lactate elimination after a respiratory muscle endurance training period. Further investigations are needed to answer this question.

Preliminary exercise and lactate elimination

It has been shown that the intensity of preliminary exercise influences kinetics of subsequent lactate elimination (17) and thus might falsify results. For the present study, data of the three arm cranking tests to exhaustion preceding the three recovery interventions refute this assumption. No differences were found in peak power, VO_{2peak}, maximal heart rate or peak lactate concentration between tests (Table 1), which implies that preceding exhaustive exercise was comparable for each testing session.

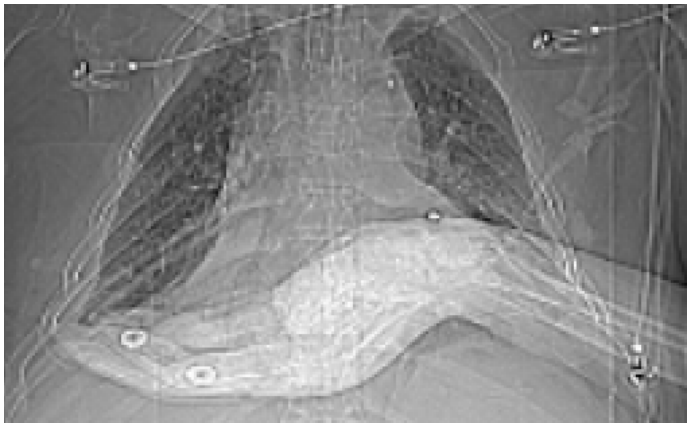
Conclusions

Low intensity isocapnic hyperpnoea seems not to enhance blood lactate disappearance after exhaustive arm exercise compared to passive or active recovery with the previously loaded muscle group. The magnitude of the involved muscle mass appears to be critical to an effective active recovery represented by the fact that also arm cranking failed to significantly enhance blood lactate elimination.

References

1. **Ahmaidi S, Granier P, Taoutaou Z, Mercier J, Dubouchaud H, Prefaut C.** Effects of active recovery on plasma lactate and anaerobic power following repeated intensive exercise. *Med Sci Sports Exerc* 28:450-456, 1996.
2. **Arora NS, Rochester DF.** Effect of body weight and muscularity on human diaphragm muscle mass, thickness, and area. *J Appl Physiol* 52:64-70, 1982.
3. **Astrand PO, Hultman E, Juhlin-Dannfelt A, Reynolds G.** Disposal of lactate during and after strenuous exercise in humans. *J Appl Physiol* 6:338-343, 1986.
4. **Beaver WL, Wasserman K, Whipp BJ.** A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 60:2020-2027, 1986.
5. **Bond V, Adams RG, Tearney RJ, Gresham K, Ruff W.** Effects of active and passive recovery on lactate removal and subsequent isokinetic muscle function. *J Sports Med Phys Fitness* 31:357-361, 1991.
6. **Borg GA.** Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 14:377-381, 1982.

7. **Brooks GA, Gaesser GA.** End points of lactate and glucose metabolism after exhausting exercise. *J Appl Physiol* 49:1057-1069, 1980.
8. **Celli B, Criner G, Rassulo J.** Ventilatory muscle recruitment during unsupported arm exercise in normal subjects. *J Appl Physiol* 64:1936-1941, 1988.
9. **Choi D, Cole KJ, Goodpaster BH, Fink WJ, Costill DL.** Effect of passive and active recovery on the resynthesis of muscle glycogen. *Med Sci Sports Exerc* 26:992-996, 1994.
10. **Dodd S, Powers SK, Callender T, Brooks E.** Blood lactate disappearance at various intensities of recovery exercise. *J Appl Physiol* 57:1462-1465, 1984.
11. **Dupont G, Blondel N, Berthoin S.** Performance for short intermittent runs: active recovery vs. passive recovery. *Eur J Appl Physiol* 89:548-554, 2003.
12. **Freund H, Oyono-Enguelle S, Heitz A, Marbach J, Ott C, Zouloumian P, et al.** Work rate-dependent lactate kinetics after exercise in humans. *J Appl Physiol* 61:932-939, 1986.
13. **Freund H, Zouloumian P.** Lactate after exercise in man: I. Evolution kinetics in arterial blood. *Eur J Appl Physiol Occup Physiol* 46:121-133, 1981.
14. **Gupta S, Goswami A, Sadhukhan AK, Mathur DN.** Comparative study of lactate removal in short term massage of extremities, active recovery and a passive recovery period after supramaximal exercise sessions. *Int J Sports Med* 17:106-110, 1996.
15. **Hermansen L, Stensvold I.** Production and removal of lactate during exercise in man. *Acta Physiol Scand* 86:191-201, 1972.
16. **Hermansen L.** Effect of acidosis on skeletal muscle performance during maximal exercise in man. *Bull Europ Physiopath Resp* 15:229-238, 1979.
17. **Johnson MA, Polgar J, Weightman D, Appleton D.** Data of the distribution of fibre types in thirty-six human muscles. An autopsy study. *J Neurol Sci* 18:111-129, 1973.
18. **Juel C.** Current aspects of lactate exchange: lactate/H+ transport in human skeletal muscle. *Eur J Appl Physiol* 86:12-16, 2001.
19. **Lieberman DA, Faulkner JA, Craig AB, Maxwell LC.** Performance and histochemical composition of guinea pig and human diaphragm. *J Appl Physiol* 34:233-237, 1973.
20. **Mador MJ, Acevedo FA.** Effect of respiratory muscle fatigue on subsequent exercise performance. *J Appl Physiol* 70:2059-2065, 1991.
21. **Martin B, Heintzelman M, Chen HI.** Exercise performance after ventilatory work. *J Appl Physiol* 52:1581-1585, 1982.
22. **McLellan TM, Skinner JS.** Blood lactate removal during active recovery related to aerobic threshold. *Int J Sports Med* 3:224-228, 1984.
23. **McLoughlin P, McCaffrey N, Moynihan JB.** Gentle exercise with a previously inactive muscle group hastens the decline of blood lactate concentration after strenuous exercise. *Eur J Appl Physiol* 62:274-278, 1991.
24. **McMaster WC, Stoddard T, Duncan W.** Enhancement of blood lactate clearance following maximal swimming. Effect of velocity of recovery swimming. *Am J Sports Med* 17:472-477, 1989.
25. **Monedero J, Donne B.** Effect of recovery interventions on lactate removal and subsequent performance. *Int J Sports Med* 21:593-597, 2000.
26. NHLBI Workshop Summary: Respiratory muscle fatigue: report of the respiratory muscle fatigue workshop group. *Am Rev Respir Dis* 142:474-480, 1990.
27. **Nindl BC, Scoville CR, Sheehan KM, Leone CD, Mello RP.** Gender differences in regional body composition and somatotrophic influences of IGF-I and leptin. *J Appl Physiol* 92:1611-1618, 2002.
28. **Sonetti DA, Wetter TJ, Pegelow DF, Dempsey JA.** Effects of respiratory muscle training versus placebo on endurance exercise performance. *Respir Physiol* 127:185-199, 2001.
29. **Spengler CM, Roos M, Laube SM, Boutellier U.** Decreased exercise blood lactate concentrations after respiratory endurance training in humans. *Eur J Appl Physiol* 79:299-305, 1999.
30. **Stamford BA, Weltman A, Moffatt R, Sady S.** Exercise recovery above and below anaerobic threshold following maximal work. *J Appl Physiol* 51:840-844, 1981.
31. **Susheela AK, Walton JN.** Note on the distribution of histochemical fibre types in some normal human muscles: A study on autopsy material. *J Neurol Sci* 8:201-207, 1969.
32. **Thiriet P, Gozal D, Wouassi D, Oumarou T, Gelas H, Lacour JR.** The effect of various recovery modalities on subsequent performance in consecutive supramaximal exercise. *J Sports Med Phys Fitness* 33:118-129, 1993.
33. **Weltman A, Stamford BA, Moffat RJ, Katch VL.** Exercise recovery, lactate removal, and subsequent performance. *Res Q* 48:786-796, 1977.



Chapter 7

Reproducibility of Computed Tomography to assess Rib Cage Mobility in Humans

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Submitted

Abstract

Background: In various health conditions such as neuromuscular diseases, rib cage mobility decreases. Changes in rib cage mobility should be measured before and after interventions to mobilize or strengthen the respiratory pump. Thus, an accurate and easy to perform test is needed.

Methods: We analyzed single slice computed tomography scans of the chest to assess the reproducibility of maximal in- and expiration in 10 able bodied individuals and 10 subjects with tetraplegia. Computed tomography scans were performed twice in the supine position, with a repositioning of subjects in-between. At maximal in- and expiration, two slices at the fourth and ninth vertebral body were recorded. Intra-costal areas, anterior-posterior distances between sternum and vertebral body as well as transversal distances were measured. Intraclass correlation coefficients and Bland & Altman plots were calculated for intra-subject reproducibility at maximal in- and expiration as well as for intra- and inter-tester reproducibility of three independent testers, each of them analyzing all data twice.

Results: Mean differences between the two measurements expressed as percent of their mean were 2.3 ± 1.3% in able bodied individuals and 2.1 ± 1.3% in subjects with tetraplegia. All intraclass correlation coefficients were above 0.95 and thus showed very high reproducibility.

Conclusion: Computed tomography of the chest is a reproducible method to assess rib cage mobility in humans.

Introduction

The coordinated action of respiratory muscles affects respiratory mechanics in humans (17). Respiratory mechanics depends on the mobility of the thoracic cage, which is determined by the compliance of the abdomen and the mobility of the rib cage. Rib cage mobility decreases in various health conditions, such as chronic obstructive pulmonary disease, ankylosing spondylitis, pulmonary emphysema, multiple sclerosis, amyotrophic lateral sclerosis, spinal cord injury or kyphoscoliosis (2, 16, 18). Decreases in rib cage mobility often become chronic and thus lead to stiffness of the whole rib cage (11) which may increase the risk for respiratory failure and further respiratory complications (7).

In order to prevent patients from rib cage stiffness or even increase rib cage mobility, many different active and passive therapeutic methods exist (12, 15, 20). To evaluate the usefulness of a certain therapy, accurate measurement methods of rib cage mobility are needed. In a clinical setting they need to be easy and fast to perform as well as comfortable for the patients. High reproducibility has to be proven and measurement errors have to be known, (3) before using a method to evaluate outcomes of different therapeutic interventions.

Several methods to assess rib cage mobility have been described in literature, such as optical mapping, (22) chest circumference measurements, (4) optoelectronic plethysmography, (1) magnetic resonance imaging (9) or computed tomography (CT) (6). They all differ in reproducibility, costs and outcome measures. Even if optical mapping and optoelectronic plethysmography may provide interesting data about respiratory mechanics, they are rather laborious to perform and quite expensive. Chest circumference measurement may be the fastest, cheapest and easiest to perform of the methods mentioned above, but outcome measures provide rather less detailed information about rib cage mobility. CT may be an interesting instrument to assess rib cage mobility especially in subjects with respiratory diseases, due to the short time of breath-holding needed for CT acquisition, which only takes about five seconds. Further, new equipment and protocols allow keeping radiation dose of single slice CT very low.

The aim of this study was to assess the reproducibility of follow up measurements from a new method to test rib cage mobility, using single slice CT scans in healthy humans and patients with known restrictions in rib cage mobility. Subjects with tetraplegia were included in this study as a group of patients with known restrictions in rib cage mobility and therefore represent an interesting group to test the reproducibility of chest CT in addition to able bodied subjects.

Methods

All subjects were recruited from the same SCI rehabilitation centre, 10 able bodied subjects from the clinic staff and 10 subjects with tetraplegia. Inclusion criteria were: men or women between 20 and 65 years of age. Subjects with tetraplegia were included if they had a motor complete cervical lesion (C) for more than one year. Exclusion criteria were: pregnancy, severe scoliosis, tracheotomy or assisted ventilation. All participants were informed about the procedures and potential risks of the study prior to giving their written informed consent. The study was approved by the local ethics committee.

We analyzed CT scans of the rib cage to assess reproducibility of maximal in- and expiration in able bodied individuals and subjects with tetraplegia. CT scans were performed on a high resolution scanner (Somatom Sensation 40; Siemens, Germany). Subjects were lying down straight in supine position with the arms adjacent to the upper body. Detailed instructions about the whole procedure were given to the subjects prior to the acquisition of images. Subjects were instructed to maximally breathe in and hold their breath until the acquisition of the first image. First of all, an anterior-posterior topogram (512-512 pixel) was assessed in order to localize the exact position of slices (Figure 1). Two slices, one at the inferior end plate of the fourth thoracic vertebral body (T4) and another at the superior end plate of the ninth thoracic vertebral body (T9) were recorded in order to get information about the mechanics of the upper and lower rib cage. For the acquisition of the two slices at T4 and T9, subjects were instructed to perform a maximal inspiration and then to hold their breath until completion of the scans (for about five seconds each). Scans were performed at 120 kV and the tube current modulated for radiation dose reduction (‘care-dose protocol’), with a slice thickness of 1mm and a field of view of 500, reconstruction Kernel B25s smooth++.

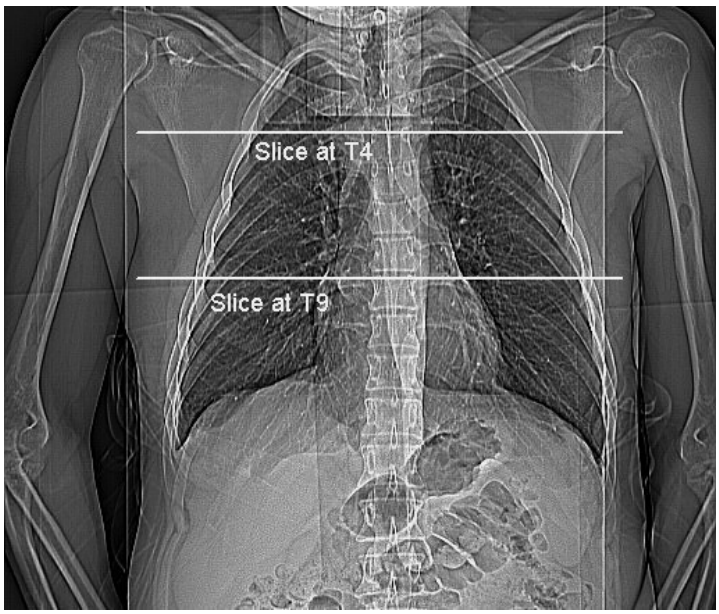

Figure 1: Topogram showing localization of slices at the fourth (T4) and ninth (T9) thoracic vertebra.

After completion of the topogram and the two slices at maximal inspiration, the whole procedure was repeated at maximal expiration. Therefore subjects were instructed to perform a maximal expiration and hold their breath until data acquisition was completed. All measurements were performed twice with a repositioning of the patient in-between, in order to calculate intra-subject reproducibility of maximal in- and expiration including possible differences from positioning. Intraclass correlation coefficients (ICCs) and Bland & Altman limits of agreement were calculated for intra-subject reproducibility at maximal in- and expiration as well as for intra- and inter-tester reproducibility of three independent testers, each of them analyzing all data twice.

Slices at maximal in- and expiration were analyzed for intra-costal areas as well as for anterior-posterior (AP) distances (between middle of inner margins of sternum and vertebral body) and transversal diameters of the rib cage by visual selection of the area and distances as shown in Figure 2. Visual selection and calculation of intra-costal (lung) areas and distances was done using 'Osiris' medical imaging software (21). Every picture was analyzed twice by three independent testers in a blinded way, with at least 24 h between the analysis in order to calculate intra- and inter-tester reproducibility.

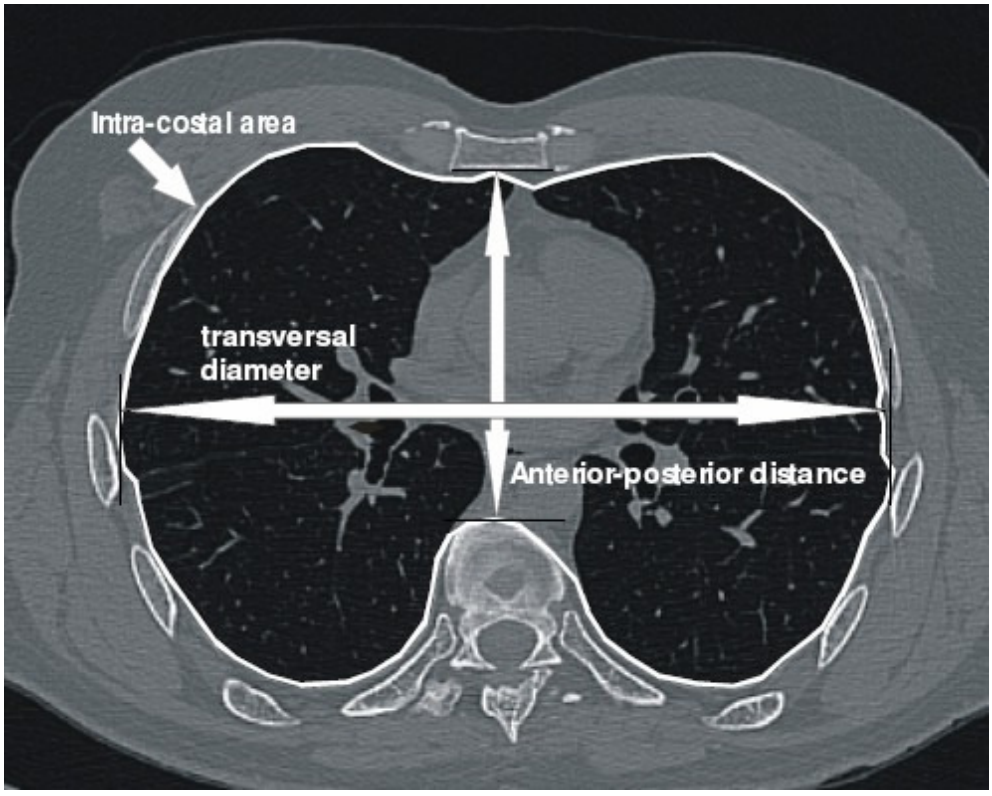

Figure 2: Single slice CT scan showing selection of intra-costal area, anterior-posterior distance between sternum and vertebral body and transversal diameter of the rib cage.

All data were analyzed by ICCs for intra-subject reproducibility as well as for intra- and inter-tester reproducibility in order to compare our data with other methods from the literature (13, 24). An ICC of 1.0 indicates that the total variance of a measurement is entirely a result of the differences between subjects, and there is no variance from the measurement method and error (8). ICCs above 0.75 generally represent acceptable reproducibility, those greater or equal to 0.90 indicate clinically valuable reproducibility (13). Intra-subject reproducibility was calculated from mean values of both calculations of all three testers by ICCs from data produced by a one-way analysis of variance (ANOVA) described in detail elsewhere (23). Data are shown as ICCs including 95% confidence intervals of ICCs. Intra-tester reproducibility was calculated from data produced from a one-way ANOVA for differences between the first and second analysis of the same pictures from all three testers together. Inter-tester reproducibility was calculated from data produced from a two-way ANOVA for all pictures analyzed by the three independent testers.

In addition, Bland & Altman plots (3) for intra-costal areas were drawn to assess the mean difference (bias) between the two scans of each patient against their mean and the limits of agreement (mean ± 2 standard deviations (SD) of the difference). The limits of agreement represent the measurements error which has to be known for a practical use of this method. Thus, changes due to an intervention have to exceed limits of agreement in order to represent real changes. Results of Bland & Altman plots are presented graphically as separate plots for intra-costal areas at T4 and T9 and at maximal in- and expiration. Separate limits of agreement for able bodied individuals and subjects with tetraplegia were calculated for intra-subject reproducibility of maximal in- and expiration, in order to assess the measurements error of all measured parameters. To compare the reproducibility of our method to other methods, we calculated differences between the two measurements as percentage of their mean for each individual subject and present these data as group means ± SD for each parameter and subjects with tetraplegia and able bodied individuals separately.

Results

Characteristics of the able bodied and the tetraplegic group did not differ significantly (Table 1).

Table 1: Means ± standard deviations of subject's characteristics of the able bodied and the tetraplegic group.

Parameter	able bodied group	tetraplegic group	p-value
sex [men/women]	8 / 2	8 / 2	-
age [years]	46.8 ± 11.5	47.4 ± 12.7	0.30
height [m]	1.77 ± 0.07	1.76 ± 0.06	0.36
body mass [kg]	80 ± 7	75 ± 12	0.13
lesion level	-	C4 - C7	-
time post injury [years]	-	13.6 ± 8.2	-

Mean differences of all measured parameters between the two measurements expressed as percent of their mean were 2.1 ± 1.3% (0.7 to 5.2 %) in subjects with tetraplegia and 2.3 ± 1.3% (0.8 to 4.7%) in able bodied individuals, representing small errors for both groups (Table 2).

Table 2: Data of Bland & Altman plots showing group means ± standard deviations, limits of agreement (± 2 SD of intra-subjects differences) and mean individual differences between the two measurements expressed as percent of their absolute mean for able bodied individuals and tetraplegic subjects separately.

	able bodied subjects			**tetraplegic subjects**		
	mean ± SD	limits of agreement	Diff. (%)	mean ± SD	limits of agreement	Diff (%)
Inspiration						
area at T4 [mm^2]	30337±5081	-2649→3511	2.3±2.7	20449±4931	-1438→910	1.8±0.6
area at T9 [mm^2]	45599±6282	-1934→2775	1.7±0.9	35162±3346	-858→1499	1.7±1.3
AP distance at T4 [mm]	101±18	-7→9	4.2±3.9	75±16	-4→5	2.3±1.6
AP distance at T9 [mm]	138±19	-6→8	4.7±4.6	108±14	-4→3	5.2±3.7
transversal diameter at T4 [mm]	246±14	-5→7	0.9±0.9	218±17	-6→5	1.1±0.6
transversal diameter at T9 [mm]	281±15	-7→8	0.9±1.1	266±14	-8→4	0.8±1.1
Expiration						
area at T4 [mm^2]	19139±7049	-2404→2415	1.9±2.0	16303±3990	-2027→2376	1.2±0.8
area at T9 [mm^2]	36248±5973	-1638→893	2.5±1.8	31183±3936	-1352→1442	1.6±1.7
AP distance at T4 [mm]	67±27	-6→7	3.0±3.4	63±11	-6→8	2.2±1.2
AP distance at T9 [mm]	111±21	-8→5	3.2±2.8	96±14	-4→5	4.2±2.7
transversal diameter at T4 [mm]	220±18	-9→9	1.6±1.3	205±19	-10→8	1.8±1.2
transversal diameter at T9 [mm]	264±12	-5→4	0.7±0.6	261±14	-6→7	0.9±0.8

SD = standard deviation; T = thoracic vertebra; AP = anterior-posterior

Intra-subject reproducibility of maximal in- and expiration was very high with ICCs between 0.97 and 0.99 in able bodied individuals and subjects with tetraplegia (Table 3). Intra-tester reproducibility was very high as well with all ICCs between 0.99 and 1.0 (Table 4). Inter-tester reproducibility, i.e. reproducibility between the three independent testers, was all between 0.97 and 1.00 and thus did not substantially influence data (Table 5).

Table 3: Results of intra-subject reproducibility showing ICCs with 95% CIs for able bodied and tetraplegic subjects.

	able bodied subjects		**tetraplegic subjects**	
	ICC	95% CI	ICC	95% CI
Inspiration				
area at T4	0.974	0.892 →0.975	0.997	0.984→0.996
area at T9	0.991	0.956 →0.990	0.993	0.956 →0.991
AP distance at T4	0.987	0.946 →0.988	0.995	0.973 →0.994
AP distance at T9	0.990	0.954 →0.990	0.996	0.987 →0.995
transversal diameter at T4	0.978	0.920→0.994	0.988	0.957→0.997
transversal diameter at T9	0.971	0.894→0.993	0.979	0.923→0.995
Expiration				
area at T4	0.992	0.970 →0.993	0.980	0.936 →0.977
area at T9	0.997	0.980 →0.997	0.991	0.971 →0.989
AP distance at T4	0.996	0.984 →0.996	0.973	0.911 →0.968
AP distance at T9	0.994	0.996 →0.994	0.994	0.980 →0.993
transversal diameter at T4	0.971	0.896→0.993	0.972	0.896→0.993
transversal diameter at T9	0.981	0.931→0.995	0.970	0.890→0.992

ICC = intraclass correlation coefficient; CI = confidence interval; T = thoracic vertebra; AP = anterior-posterior

Table 4: Results of intra-tester reproducibility showing ICCs with 95% CIs for able bodied and tetraplegic subjects.

	able bodied subjects		**tetraplegic subjects**	
	ICC	95% CI	ICC	95% CI
Inspiration				
area at T4	1.000	1.000 →1.000	1.000	1.000 →1.000
area at T9	1.000	1.000 →1.000	1.000	0.999 →1.000
AP distance at T4	0.999	0.995 →0.998	1.000	0.999 →1.000
AP distance at T9	0.999	0.997 →0.999	0.999	0.997 →0.999
transversal diameter at T4	0.999	0.997→1.000	0.998	0.991→0.999
transversal diameter at T9	0.996	0.986→0.999	0.997	0.990→0.999
Expiration				
area at T4	1.000	1.000 →1.000	1.000	1.000 →1.000
area at T9	1.000	1.000 →1.000	0.999	0.997 →0.999
AP distance at T4	1.000	0.999 →1.000	0.999	0.996→0.999
AP distance at T9	0.999	0.998 →0.999	0.999	0.997 →0.999
transversal diameter at T4	0.998	0.991→0.999	0.999	0.995→1.000
transversal diameter at T9	0.994	0.977→0.998	0.994	0.977→0.998

ICC = intraclass correlation coefficient; CI = confidence interval; T = thoracic vertebra; AP = anterior-posterior

Table 5: Results of inter-tester reproducibility showing ICCs with 95% CIs for able bodied and tetraplegic subjects.

	able bodied subjects		**tetraplegic subjects**	
	ICC	95% CI	ICC	95% CI
Inspiration				
area at T4	1.000	0.999 →1.000	0.997	0.989 →0.998
area at T9	1.000	0.999 →1.000	1.000	0.999 →1.000
AP distance at T4	0.999	0.997 →0.999	0.997	0.993 →0.998
AP distance at T9	0.995	0.991 →0.997	0.999	0.997 →0.999
transverse diameter at T4	0.998	0.993→0.999	0.995	0.986→0.999
transverse diameter at T9	0.947	0.860→0.985	0.983	0.953→0.995
Expiration				
area at T4	1.000	0.994 →1.000	0.998	0.972 →0.998
area at T9	1.000	0.999 →1.000	0.999	0.996 →0.999
AP distance at T4	0.999	0.998 →0.999	0.998	0.997→0.999
AP distance at T9	0.999	0.998 →0.999	0.999	0.998 →0.999
transverse diameter at T4	0.996	0.989→0.999	0.976	0.935→0.994
transverse diameter at T9	0.996	0.990→0.999	0.976	0.934→0.993

ICC = intraclass correlation coefficient; CI = confidence interval; T = thoracic vertebra; AP = anterior-posterior

Additional information about reproducibility of maximal in- and expiration of able bodied individuals and subjects with tetraplegia is presented by Bland & Altman plots for intra-costal areas in Figures 3a-d. Mean differences show that there is no systematic error in the assessments of intra-costal areas (Figure 3).

Fig. 3a)

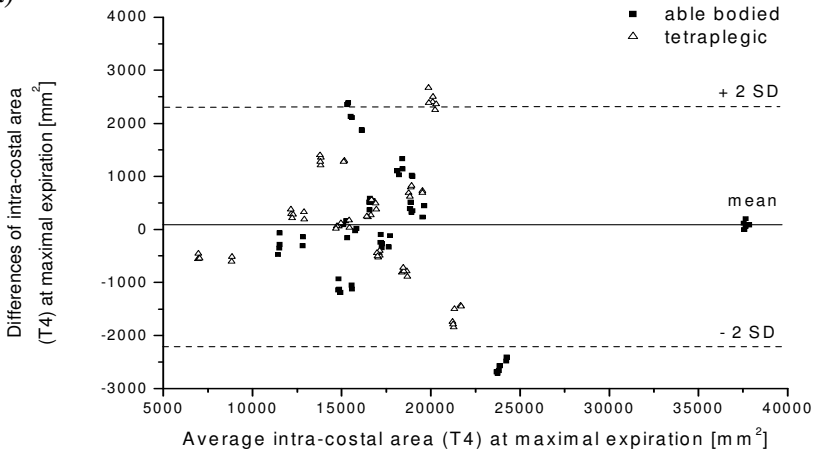

Fig. 3b)

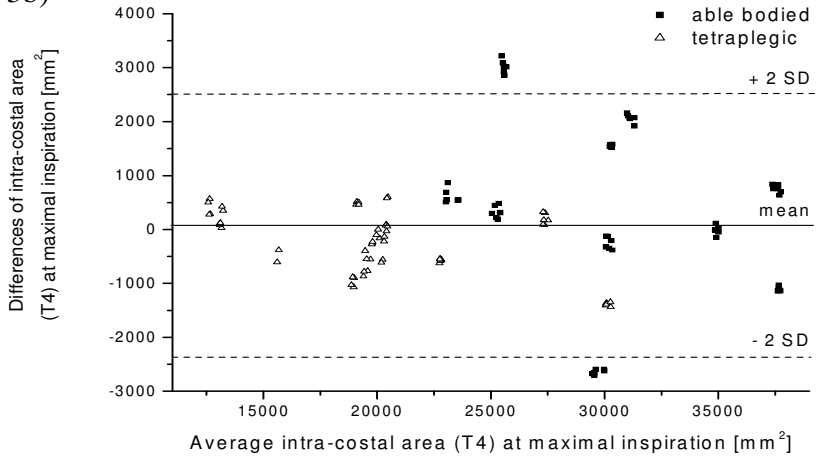

Fig. 3c)

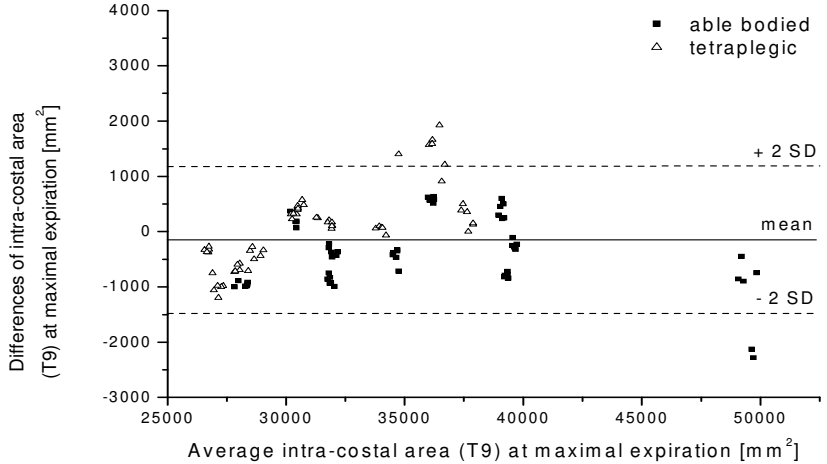

Fig. 3d)

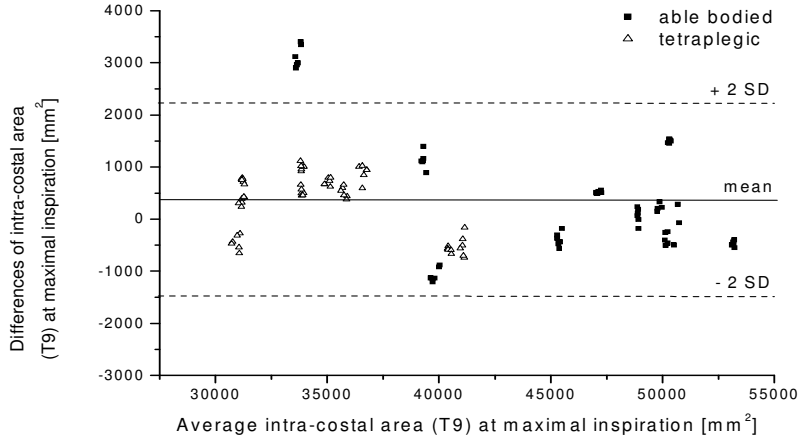

Figure 3a-d: Bland & Altman plots showing intra-subject reproducibility of intra-costal area in able bodied subjects and subjects with tetraplegia at maximal expiration (Figures 3a + 3c) and at maximal inspiration (Figures 3b + 3d). The solid lines represent the mean difference between the first and second measurement. The two dashed lines graphically represent the limits of agreement (± 2 SD) for able bodied and tetraplegic subjects as one group. Abbreviations: T4 = fourth thoracic vertebra; T9 = ninth thoracic vertebra.

Discussion

This study showed that single slice CT provides a reliable assessment tool for follow up measurements of rib cage mobility in humans. CT is clinically established and easy to perform. Intra-subject reproducibility of this method was shown to be excellent with ICCs all at or above 0.97. Mean difference between the two measurements expressed as % of their mean was 2.1 ± 1.3% in subjects with tetraplegia and 2.3 ± 1.3% in able bodied individuals, supporting a high reproducibility of the method presented and evaluated in this paper.

Reproducibility

Reproducibility of the measurement method is of high importance for practical use of rib cage mobility measurements in before-after trials or to assess courses of diseases. Until today, several measurement methods have been evaluated and described in literature (1, 22). Optical mapping is rather laborious to perform and was only evaluated for the reproducibility of volume measurements but not for rib cage mobility (22). Morgan et al. found a 5% underestimate in vital capacity from the flow volume loop by optical mapping and an up to 10% margin within subject systematic error (22). A rather new and very interesting method to assess rib cage mobility is optoelectronic plethysmography (1). Even if discrepancies between spirometry and optoelectronic plethysmography was only 1.7 ± 5.9%, the required equipment is quite expensive and the method is rather laborious and time consuming to operate (1). Chest circumference measurement is a very common and easily performed method to assess rib cage mobility (4, 14, 19). Its reproducibility has been tested in a very similar way to the present study, but in a very small sample of about five subjects. Even though they reported high ICCs between 0.81 and 0.91, the range of thoracic excursions between maximal in- and expiration was high (1.0 to 7.8 cm). Compared to that the mean SD of 0.6 cm is considerable (4), which puts the sensitivity of this method into question. An intervention study with asthma patients assessed changes by chest circumference measurements and reported mean increases of 0.8 cm and 0.9 cm of the lower and upper thoracic excursions (5). Compared to the methods described in literature, mean differences between the two measurements in our study are rather small. Reproducibility of the intra-costal area and transverse diameters was very high with differences of 0.7 to 2.5% of their mean (Table 1). Therefore the reproducibility of our method is even better than optoelectronic plethysmography which showed a mean error of 1.7 ± 5.9% (1). Due to the very high reproducibility, we conclude that our method is useful to detect even small changes in follow up measurements of rib cage mobility.

Rib cage mechanics

Compared to chest circumference measurements, CT provides interesting additional possibilities to study rib cage mechanics. The slice at T4 was chosen in order to get information about the function of respiratory muscles of the upper thorax and neck and its influence on rib cage mobility. The scalenes for example are known to expand the rib cage and the lung (10). Thus, increased strength of the scalenes would be apparent in area and/or distances at the T4 level. The slice at T9 was chosen in order to show consequences of diaphragmatic and intra-costal muscle action on rib cage motion. Especially in subjects with diseases that lead to rib cage stiffening and changes in compliance of the whole respiratory system, e.g. in tetraplegia, additional information from the measurement at T9 may help to assess rib cage mobility more precisely.

Limitations

We are aware of the fact that there is a certain radiation dose applied to individuals during CT measurements used in this study. Taking this into account, we used a so called 'care dose protocol' where radiation dose is kept as low as possible and we only recorded four slices of the rib cage. The radiation dose of our protocol (four slices) is comparable to four transatlantic flights, which should not give any cause for concern.

Clinical relevance

Our method provides an easy and fast to perform tool for the precise measurement of rib cage mobility. For future practical use, e.g. for reporting possible effects of different interventions on rib cage mobility, limits of agreement should be taken into account as measurements error (3). Thus, possible changes in before-after trials of intra-costal area, AP distances and transverse diameters at maximal in- and expiration have to exceed limits of agreement to represent real changes. In order to reach the maximal reproducibility in practice, some learning trials of maximal in- and expiration manoeuvres are recommended. Reproducibility can even be increased if all pictures within one subject are analysed by the same tester, although intra-tester reproducibility is very high.

Conclusion

Single slice chest CT is a reliable method for follow up measurements, to assess rib cage mobility in humans, with all ICCs at or above 0.95. The low mean differences between the two measurements confirm that our method is even better than those with the highest reproducibility among the methods described in literature.

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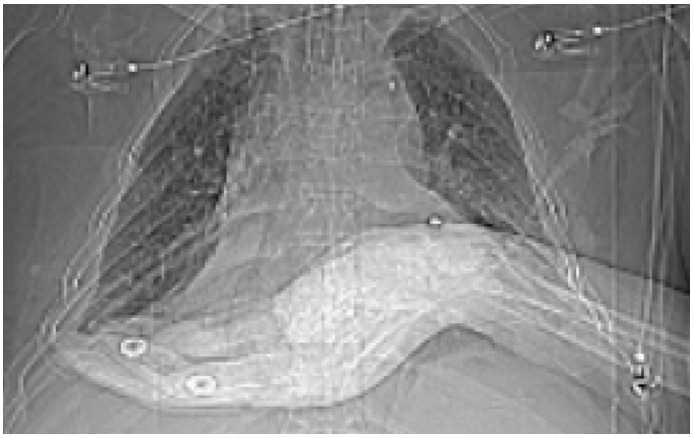
References

1. **Aliverti A, Cala SJ, Duranti R, Ferrigno G, Kenyon CM, Pedotti A, Scano G, Sliwinski P, Macklem PT, and Yan S**. Human respiratory muscle actions and control during exercise. *J Appl Physiol* 83: 1256-1269, 1997.
2. **Ben-Haim SA, and Saidel GM**. Chest wall mechanics: effects of acute and chronic lung disease. *J Biomech* 22: 559-564, 1989.
3. **Bland JM, and Altman DG**. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1: 307-310, 1986.
4. **Bockenhauer SE, Chen H, Julliard KN, and Weedon J**. Measuring thoracic excursion: reliability of the cloth tape measure technique. *J Am Osteopath Assoc* 107: 191-196, 2007.
5. **Bockenhauer SE, Julliard KN, Lo KS, Huang E, and Sheth AM**. Quantifiable effects of osteopathic manipulative techniques on patients with chronic asthma. *J Am Osteopath Assoc* 102: 371-375; discussion 375, 2002.
6. **Brown MS, McNitt-Gray MF, Goldin JG, Greaser LE, Hayward UM, Sayre JW, Arid MK, and Aberle DR**. Automated measurement of single and total lung volume from CT. *J Comput Assist Tomogr* 23: 632-640, 1999.
7. **Brown R, DiMarco AF, Hoit JD, and Garshick E**. Respiratory dysfunction and management in spinal cord injury. *Respir Care* 51: 853-868;discussion 869-870, 2006.
8. **Chien PF, Owen P, and Khan KS**. Validity of ultrasound estimation of fetal weight. *Obstet Gynecol* 95: 856-860, 2000.
9. **Cluzel P, Similowski T, Chartrand-Lefebvre C, Zelter M, Derenne JP, and Grenier PA**. Diaphragm and chest wall: assessment of the inspiratory pump with MR imaging-preliminary observations. *Radiology* 215: 574-583, 2000.
10. **De Troyer A, and Estenne M**. Coordination between rib cage muscles and diaphragm during quiet breathing in humans. *J Appl Physiol* 57: 899-906, 1984.
11. **Estenne M, Heilporn A, Delhez L, Yernault JC, and De Troyer A**. Chest wall stiffness in patients with chronic respiratory muscle weakness. *Am Rev Respir Dis* 128: 1002-1007, 1983.
12. **Estenne M, Knoop C, Vanvaerenbergh J, Heilporn A, and De Troyer A**. The effect of pectoralis muscle training in tetraplegic subjects. *Am Rev Respir Dis*139: 1218-1222, 1989.
13. **Fleiss JL**. Reliability of measurement. In: *Design and analysis of clinical experiments*, edited by Fleiss JL. New York: John Wiley & Sons, 1986, p. 1-32.
14. **Fregonezi GA, Resqueti VR, Guell R, Pradas J, and Casan P**. Effects of 8-week, interval-based inspiratory muscle training and breathing retraining in patients with generalized myasthenia gravis. *Chest* 128: 1524-1530, 2005.
15. **Gallego J, Perez de la Sota A, Vardon G, and Jaeger-Denavit O**. Learned activation of thoracic inspiratory muscles in tetraplegics. *Am J Phys Med Rehabil / Assoc Acad Physiatr* 72: 312-317, 1993.
16. **Gilmartin JJ, and Gibson GJ**. Mechanisms of paradoxical rib cage motion in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 134: 683-687, 1986.
17. **Han JN, Gayan-Ramirez G, Dekhuijzen R, and Decramer M**. Respiratory function of the rib cage muscles. *Eur Respir J* 6: 722-728, 1993.
18. **Haslock I**. Ankylosing spondylitis. *Baillieres Clin Rheumatol* 7: 99-115, 1993.
19. **Kakizaki F, Yamazaki T, and Suzuki H**. Preliminary report on the effects of respiratory muscle stretch gymnastics on chest wall mobility in patients with chronic obstructive disease. *Respir Care* 44: 409-414, 1999.
20. **Liaw MY, Lin MC, Cheng PT, Wong MK, and Tang FT**. Resistive inspiratory muscle training: its effectiveness in patients with acute complete cervical cord injury. *Arch Phys Med Rehabil* 81: 752-756, 2000.
21. **Ligier Y, Ratib O, Logean M, and Girard C**. Osiris: a medical image-manipulation system. *MD Comput* 11: 212-218, 1994.

22. **Morgan MD, Gourlay AR, and Denison DM**. An optical method of studying the shape and movement of the chest wall in recumbent patients. *Thorax* 39: 101-106, 1984.
23. **Rankin G, and Stokes M**. Reliability of assessment tools in rehabilitation: an illustration of appropriate statistical analyses. *Clin Rehabil* 12: 187-199, 1998.
24. **Shrout PE, and Fleiss JL**. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 86: 420-428, 1979.



Chapter 8

Rib Cage Mobility of Individuals with Chronic Tetraplegia is Reduced but not Absent, whereas Mobility of the Diaphragm is Intact

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Claudio Perret

Franz Michel

Markus Berger

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Submitted

Abstract

Objective: Due to respiratory muscle paralysis chest wall mechanics is severely altered in individuals with tetraplegia. The aim of this study was to compare mobility of the rib cage and the diaphragm between able bodied persons and individuals with chronic tetraplegia with lesions between C5 and C8.

Methods: 10 able bodied and 10 motor complete chronic tetraplegic individuals, matched for gender, age and height, participated in the study. All individuals underwent lung function testing and computed tomography of the thorax. At maximal in- and expiration, an overview of the thorax and two slices at the bottom plate of the fourth thoracic vertebra (T4) and the cover plate of the ninth thoracic vertebra (T9) were recorded. Differences between maximal inspiration and maximal expiration for diaphragm and rib cage mobility were calculated.

Results: Rib cage mobility was significantly higher in able bodied than in tetraplegic individuals for Δ intra-costal area at T4: 100 cm^2 (CI 69-132 cm^2) vs. 39 cm^2 (CI 19-60 cm^2), Δ intra-costal area at T9: 118 cm^2 (CI 83-152 cm^2) vs. 49 cm^2 (CI 18-79 cm^2), Δ anterior-posterior distance at T4: 2.8 cm (CI 1.6-3.9 cm) vs. 1.2 cm (CI 0.5-2.0 cm), Δ anterior-posterior distance at T9: 3.4 cm (CI 2.2-4.5 cm) vs. 1.4 cm (CI 0.5-2.3 cm) and Δ transverse diameter at T4: 1.8 cm (CI 1.3-2.2 cm) vs. 0.2 (CI -0.2-0.7 cm). Diaphragm mobility and Δ transverse diameter at T9 showed no significant differences between able bodied and tetraplegic subjects: 5.2 cm (CI 3.8-6.6 cm) vs. 4.9 cm (CI 3.5-6.0 cm) and 2.6 cm (CI 1.8-3.5 cm) vs. 1.4 cm (CI 0.6-2.2 cm).

Conclusion: This study showed that compared to able bodied individuals, rib cage mobility of chronic, motor complete tetraplegic individuals is significantly reduced but still present, while complicance of the diaphragm has not altered compared to able bodied individuals.

Introduction

Mobility of the chest wall is an important determinant of breathing capacity in humans (17). Chest wall mobility is determined by the mobility of the rib cage and the abdominal compliance. Rib cage mobility can be decreased due to various respiratory diseases and cause further problems resulting in pulmonary complications (4, 15, 18). In individuals with tetraplegia, decreases in rib cage mobility mainly occur due to the loss of inter-costal muscle innervation (11). With ongoing lesion duration the rib cage stiffens, which consequently leads to additional impairments in pulmonary function (16). The high rate of respiratory complications in individuals with tetraplegia and the concomitant high mortality rate of 24% who die due to complications of the respiratory system, may also be influenced by impairments in rib cage mobility (6).

It is known that in individuals with tetraplegia lung function and respiratory muscle strength is decreased compared to able bodied persons (3, 14, 23, 25). Nevertheless, Morgan et al. found that total chest wall displacement could not be predicted from vital capacity (20). Thus, sensitivity of lung function testing is not specific enough to assess breathing mechanics in subjects with tetraplegia. We recently evaluated a new method to assess rib cage mobility by single slice computed tomography (CT) which is easy and fast to perform. Intra-subject as well as intra- and inter-tester reproducibility were shown to be high (Chapter 7) (22).

The aim of this study was to quantify differences of upper and lower rib cage mobility as well as diaphragm movement between able bodied persons and individuals with chronic tetraplegia, and to set these differences in relation to spirometry. Detailed knowledge of differences between able bodied and tetraplegic individuals may contribute to a better understanding of altered breathing mechanics in tetraplegic individuals. Possible changes in rib cage mobility due to respiratory interventions should then be quantified and set in relation to able bodied values. This may help to apply the most adequate interventions aiming at increased rib cage mobility.

Methods

Ten individuals with tetraplegia were recruited from one spinal cord injury rehabilitation clinic. For each participant with tetraplegia, one able bodied subject of the same gender and comparable age (± 2 years) and height (± 2 cm) was recruited from the clinic staff in order to build matched-pairs. Inclusion criteria were: healthy men and women, aged between 20 and 65 years. Individuals with tetraplegia were included if they had a motor complete cervical (C) lesion for more than one year. Exclusion criteria were: pregnancy, severe scoliosis, tracheostomy, assisted ventilation, chronic obstructive pulmonary disease, actual respiratory tract infection or any other respiratory disease. The study was approved by the local ethics committee. All participants were informed about the procedures and potential risks of the

study, prior to giving their written informed consent. Individuals were asked to abstain from caffeine intake on all test days (26).

Lung function testing

The first session included lung function and respiratory muscle pressure measurements in the sitting position, according to the standards of the American Thoracic Society (1) by means of bodyplethysmography (MasterScreen Body, Jaeger, Hoechberg, Germany). Total lung capacity (TLC), residual volume (RV), expiratory reserve volume, functional residual capacity (FRC), forced vital capacity (FVC), forced expiratory volume in 1 s, peak expiratory flow and maximal voluntary ventilation during 12 s were measured. The whole system was calibrated immediately before each test. Maximal inspiratory muscle pressure over 1 s was measured from RV and maximal expiratory muscle pressure was measured from TLC (MicroRPM, MicroMedical Limited, Kent, UK). A small air leak in the measurement device prevented glottis closure.

Computed tomography (CT)

Computed tomography scans were performed according to the method described in chapter 7. Additionally, the raw data for diaphragatic movement were calculated by visual selection of the left and right diaphragmatic dome at maximal in- and expiration (Figure 1). Coordinates of the diaphragmatic dome were imported to a self-written excel program and the vertical distance between the highest points at maximal in- and expiration were defined as diaphragmatic movement (Figure 1).

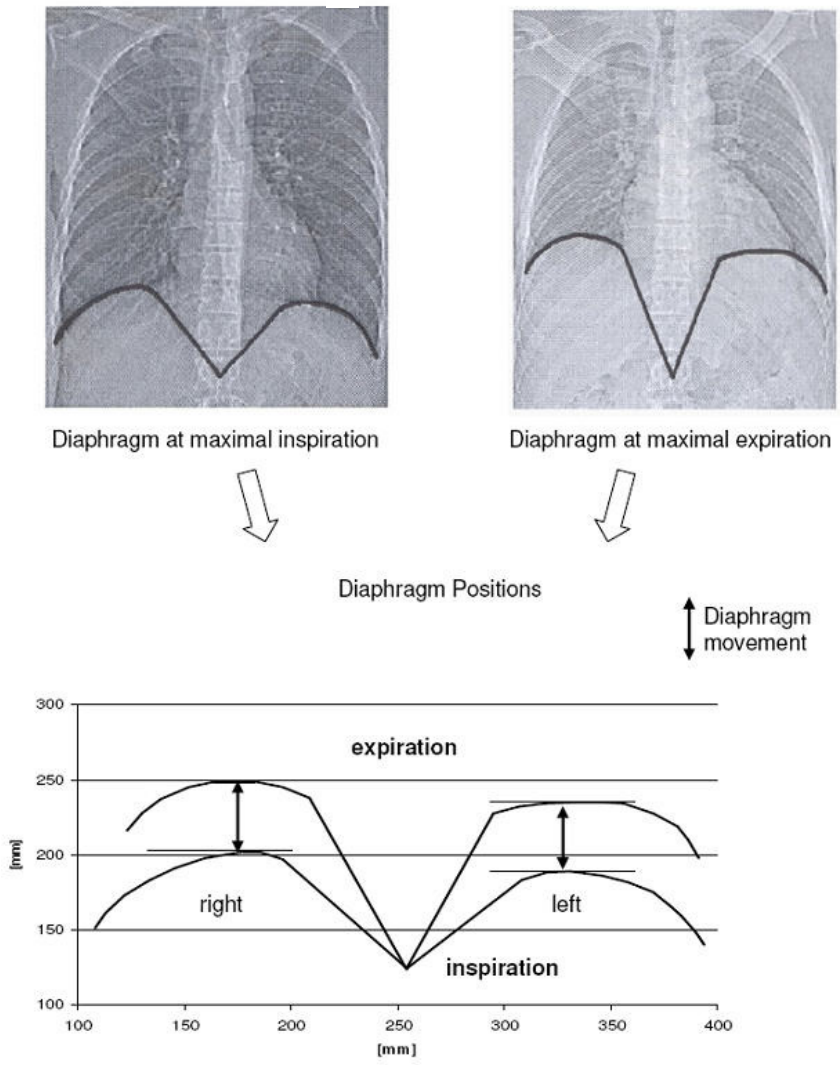

Figure 1: Calculation of diaphragmatic movement as the vertical distance between top positions of the diaphragm at maximal inspiration and maximal expiration. The same spinal process on both images was chosen as reference point in order to overlay the two images.

Statistics

Results of individuals' characteristics, lung function and respiratory muscle pressure measurements are given as mean ± SD. Results of diaphragm and rib cage mobility are presented as means with 95% confidence intervals (CI). Differences between maximal in- and expiration, i.e. diaphragm movement (left and right separately), AP distances and transverse diameter at T4 and T9, as well as intra-costal areas at T4 and T9, were calculated for each subject. Means and 95% CI for these parameters of the able bodied and the tetraplegic groups were calculated separately as well. Differences of all measured parameters between matched pairs of able bodied individuals and individuals with tetraplegia were calculated by Wilcoxon rank-sum-tests using Systat, (Systat Software Inc.; Version 10.2; Point Richmond CA; USA). Significance level was set at $p < 0.05$.

Results

There were no significant differences for age, height and weight between the matched-pairs groups (Table 1).

Table 1: Comparison of subjects' characteristics (group means ± standard deviations) of able bodied individuals and subjects with tetraplegia.

Parameter	individuals with tetraplegia	able bodied individuals	p value
age [years]	47.4 ± 12.7	46.8 ± 11.5	0.30
height [m]	1.76 ± 0.06	1.77 ± 0.07	0.36
weight [kg]	75 ± 12	80 ± 7	0.13
gender	8 m / 2 w	8 m / 2 w	
time post injury [years]	13.6 ± 8.2	-	

Lung function was measured in the sitting position and showed significantly lower lung volumes and respiratory muscle pressure in individuals with tetraplegia compared to able bodied persons, with the exception of non-significant differences in RV. Expressed as percentage of TLC, RV was 41.5% in individuals with tetraplegia and 31.5% in able bodied persons (Table 2). FRC relative to TLC did not differ between the two groups and was 53.7% in individuals with tetraplegia and 52.2% in the able bodied group (Table 2).

Table 2: Comparison of lung function and respiratory muscle pressure parameters (group means ± standard deviations) of able bodied individuals and subjects with tetraplegia.

Parameter	individuals with tetraplegia [n = 10]	able bodied individuals [n = 10]	p value
TLC [l]	5.47 ± 1.14	7.90 ± 1.42	0.007*
RV [l]	2.27 ± 0.87	2.49 ± 0.40	0.72
ERV [l]	0.67 ± 0.32	1.63 ± 0.92	0.011*
FRC [l]	2.94 ± 0.88	4.12 ± 1.13	0.037*
FVC [l]	2.91 ± 1.13	5.31 ± 1.29	0.005*
FEV_1 [l/s]	2.52 ± 1.17	4.18 ± 1.07	0.005*
PEF [l/s]	4.85 ± 2.77	8.13 ± 2.17	0.013*
MVV [l/min]	95.2 ± 55.0	159.1 ± 53.7	0.005*
MIP [kPa]	8.43 ± 4.41	11.37 ± 2.35	0.037*
MEP [kPa]	7.06 ± 2.74	14.90 ± 3.72	0.008*

* = significant difference between groups; TLC = total lung capacity; RV = residual volume; ERV = expiratory reserve volume; FRC = functional residual capacity; FVC = forced vital capacity; FEV_1 = forced vital capacity in 1 s; PEF = peak expiratory flow; MVV = maximal voluntary ventilation; MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure

No significant differences in diaphragm movement between able bodied and tetraplegic individuals were found by CT topograms. In contrast to this, all parameters of rib cage mobility at T4 were significantly lower in the tetraplegic than in the able bodied group (Table 3). Mean changes of intra-costal areas and AP distances of tetraplegic individuals were all around 40% (39-43%) of the able bodied individuals' values. Changes in mean transverse diameter between maximal in- and expiration of tetraplegic individuals at T4 was only 11% of the able bodied groups' mean. At T9 solely the changes in intra-costal areas and AP distances were lower in individuals with tetraplegia, but no significant differences were seen between able bodied and tetraplegic subjects concerning changes of the transverse diameter (Table 3). Mean changes in transverse diameter of the tetraplegic group was 54% of the mean able bodied value.

Table 3: Means (95% confidence intervals) for diaphragm movement and rib cage mobility at T4 and T9 in individuals with tetraplegia and able bodied persons.

Parameter		**individuals with tetraplegia**	**able bodied individuals**	**p value**
Diaphragm movement	right [cm]	4.6 (3.5-5.7)	5.2 (3.8-6.6)	0.44
	left [cm]	4.9 (3.8-6.0)	5.2 (3.8-6.6)	0.65
T4	Δ intra costal area [cm^2]	39 (19-60)	100 (69-132)	0.009*
	Δ AP distance [cm]	1.2 (0.5-2.0)	2.8 (1.6-3.9)	0.028*
	Δ transverse diameter [cm]	0.2 (-0.2-0.7)	1.8 (1.3-2.2)	0.005*
T9	Δ intra costal area [cm^2]	49 (18-79)	118 (83-152)	0.017*
	Δ AP distance [cm]	1.4 (0.5-2.3)	3.4 (2.2-4.5)	0.013*
	Δ transverse diameter [cm]	1.4 (0.6-2.2)	2.6 (1.8-3.5)	0.093

T = thoracic; AP = anterior-posterior; * = significant difference between groups ($p < 0.05$) Δ = difference between maximal in- and expiration

Discussion

The most important finding of this study is that, in contrast to others (10, 21), we did not find any decrease in AP diameter during inspiration, showing that no paradoxical breathing pattern was present in the 10 chronic tetraplegic individuals tested. Further, diaphragm movements and RV showed no significant differences between tetraplegic individuals and able bodied persons, representing a fully intact diaphragmatic function in motor complete tetraplegics with C5 to C8 lesions. It also seems that the 'piston effect' and the appositional effect of the diaphragm on the thoracic wall are still present in subjects with chronic tetraplegia.

Diaphragm mobility

In the supine position, there seems to be no altered force-length relationship of the diaphragm, since our results showed no differences in diaphragm mobility between tetraplegic and able bodied individuals. According to changes in the transversus distance at T9, it seems that the 'piston effect' and the appositional effect of the diaphragm on the thoracic wall are still present in subjects with chronic tetraplegia. These effects occur in spite of a diminished fulcrum function of the abdominal content due to the paralysed anterior abdominal wall and in spite of the possible stiffness of the rib cage. FVC in individuals with tetraplegia was shown to be higher in the supine than in the sitting position (12), and trans-diaphragmatic pressures at end expiration was reported to be normal in tetraplegic individuals (9). This finding supports our data, indicating that diaphragmatic function is more or less maintained after a lesion below the fifth cervical spinal cord.

In the sitting position diaphragmatic movement mainly determines FVC and depends on the resting position of the diaphragm, i.e. FRC (8). In individuals with motor complete tetraplegia, the abdomen is highly compliant due to the absence of abdominal muscle innervation (27). Thus, the diaphragm is less pushed up by the abdominal content than in the supine position. Therefore, the capacity of the diaphragm to move caudally may be impaired (5). The flattened diaphragmatic position and a concomitant shift in muscle fibre orientation causes some loss of the expiratory effect of the diaphragm in tetraplegic individuals (7). Nevertheless, in the chronic stage of a tetraplegia the diaphragm may adapt to this altered situation to regain a better force-length relationship.

Rib cage mobility

Chronic tetraplegia is represented by rib cage stiffening (13, 16), which is confirmed by the lower rib cage mobility in tetraplegic compared to able bodied individuals in the present study. While others (16) found a reduced mobility of the rib cage to about 66% of the mobility of able bodied individuals in subjects with stable tetraplegia, mean changes in intra-costal area and AP distances of tetraplegic individuals in the present study were only around 40% of the mean able bodied group values (Table 3). In this previous study subjects were between 4 month and 4 years after injury (16), while our subjects were at least one year post injury with a mean lesion duration of 13.6 years. The lower, but still not absent rib cage mobility in our subjects supports the assumption that the rib cage stiffens with ongoing lesion duration.

It is evident that in able bodied individuals a higher difference at T9 than at T4 between maximal in- and expiration of all measured parameters was present (Table 3). In individuals with tetraplegia only the transverse distance at T9 showed higher changes than parameters at T4, between maximal in- and expiration. This supports our finding of a nearly intact

diaphragmatic movement in individuals with tetraplegia in the supine position, and the appositional effect of the diaphragm as an extensor of the lower thoracic wall through the zone of apposition (7, 24). Due to gravitational forces, this expanding action may have larger effects on the transverse diameter than on the AP distance in the supine position. Taking the commonly known paradoxical breathing pattern of individuals with tetraplegia into account (13), the contracting diaphragm may pull the upper rib cage inward. Due to the lack of intercostal and abdominal muscle function this would be represented by negative AP distances at T4 between maximal in- and expiration. Since we found no such effects, stiffening may have limited paradoxical motion of the rib cage in our subjects with chronic tetraplegia. Thus, stiffening of the rib cage may also serve as an advantage (16). On the other hand, in individuals with tetraplegia, the upper part of the rib cage may gain volume due to an increased strength of the Mm. scalenes and Mm. sternocleidomastoids which pulls the upper rib cage up and outward. This may probably be improved by respiratory muscle training, if it is applied before the rib cage stiffened.

Respiratory function

Our results demonstrate a typically restrictive breathing pattern in the tetraplegic group (2) which may be caused by a lower inspiratory drive and the absence of innervations of the main expiratory muscles. The only parameter without a significant difference between able bodied and tetraplegic individuals was RV. Generally, RV is known to be higher in individuals with tetraplegia due to the lack of expiratory muscle innervation and a concomitant decrease or absence of expiratory reserve volume (3, 14). Nevertheless, relative to TLC, which is also significantly lower in tetraplegic compared to able bodied subjects, RV was 10% higher in the tetraplegic group compared to able bodied individuals (41.5 vs. 31.5%). FRC was significantly reduced in tetraplegic compared to able bodied persons (Table 2). These findings may be due to a decrease in the outward pull of the rib cage resulting from the loss of intercostal muscle activity in individuals with tetraplegia (9).

Clinical relevance

This study provides data quantifying the absolute differences of upper and lower rib cage mobility between individuals with tetraplegia and able bodied persons. These data can be seen as ‘baseline’ values to compare rib cage mobility of other groups of patients, but also to set changes due to specific respiratory interventions in relation to differences between the two groups. In order to maintain or even increase rib cage mobility in tetraplegic individuals, we postulate that interventions such as physiotherapy and respiratory muscle training should start as early as possible after injury to avoid stiffening. Furthermore such an intervention should concentrate on training of the accessory respiratory muscles and not only on the diaphragm.

Passive interventions in order to maintain mobility of the rib cage and to prevent stiffening may be indicated, especially in subjects who are not able or willing to perform active respiratory interventions.

Conclusion

This study showed that rib cage mobility of individuals with chronic, motor complete tetraplegia is significantly reduced to about 40% of the mobility of able bodied individuals, but the rib cage still moves. In contrast to earlier studies, we did not find a paradoxical breathing pattern and the 'piston effect' as well as the appositional effect of the diaphragm on the thoracic wall are still present in individuals with chronic tetraplegia. Movements of the thoracic wall in subjects with tetraplegia may primarily be caused by diaphragmatic function which did not show any significant differences to able bodied individuals. This study provides data of absolute differences in rib cage mobility and diaphragmatic movement between able bodied and tetraplegic subjects, which can be used for tetraplegic individuals to set changes in rib cage mobility in relation to able bodied individuals.

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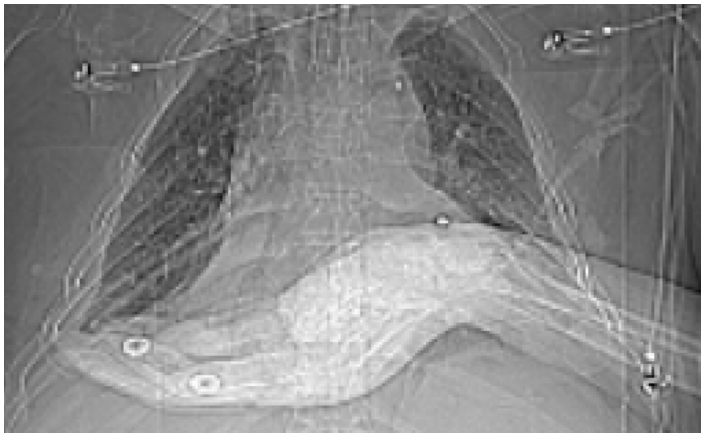
References

1. Standardization of Spirometry, 1994 Update. American Thoracic Society. *Am J Respir Crit Care Med* 152: 1107-1136, 1995.
2. **ACSM**. ACSM's guidelines for exercise testing and prescription. Baltimore: American College of Sports Medicine, 2000, p. 368.
3. **Anke A, Aksnes AK, Stanghelle JK, and Hjeltnes N**. Lung volumes in tetraplegic patients according to cervical spinal cord injury level. *Scand J Rehab Med* 25: 73-77, 1993.
4. **Ben-Haim SA, and Saidel GM**. Chest wall mechanics: effects of acute and chronic lung disease. *J Biomech* 22: 559-564, 1989.
5. **Braun NM, Arora NS, and Rochester DF**. Force-length relationship of the normal human diaphragm. *J Appl Physiol* 53: 405-412, 1982.
6. **Brown R, DiMarco AF, Hoit JD, and Garshick E**. Respiratory dysfunction and management in spinal cord injury. *Respir Care* 51: 853-868;discussion 869-870, 2006.
7. **De Troyer A**. The mechanism of the inspiratory expansion of the rib cage. *J Lab Clin Med* 114: 97-104, 1989.
8. **De Troyer A, and Estenne M**. Functional anatomy of the respiratory muscles. *Clin Chest Med* 9: 175-193, 1988.
9. **De Troyer A, and Heilporn A**. Respiratory mechanics in quadriplegia. The respiratory function of the intercostal muscles. *Am Rev Respir Dis* 122: 591-600, 1980.
10. **Derenne JP, Macklem PT, and Roussos C**. The respiratory muscles: mechanics, control, and pathophysiology. *Am Rev Respir Dis* 118: 119-133, 1978.

11. **Estenne M, and De Troyer A**. The effects of tetraplegia on chest wall statics. *Am Rev Respir Dis* 134: 121-124, 1986.
12. **Estenne M, and De Troyer A**. Mechanism of the postural dependence of vital capacity in tetraplegic subjects. *Am Rev Respir Dis* 135: 367-371, 1987.
13. **Estenne M, Yernault JC, and De Troyer A**. Rib cage and diaphragm-abdomen compliance in humans: effects of age and posture. *J Appl Physiol* 59: 1842-1848, 1985.
14. **Forner JV**. Lung volumes and mechanics of breathing in tetraplegics. *Paraplegia* 18: 258-266, 1980.
15. **Gilmartin JJ, and Gibson GJ**. Mechanisms of paradoxical rib cage motion in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 134: 683-687, 1986.
16. **Goldman JM, Williams SJ, and Denison DM**. The rib cage and abdominal components of respiratory system compliance in tetraplegic patients. *Eur Respir J* 1: 242-247, 1988.
17. **Han JN, Gayan-Ramirez G, Dekhuijzen R, and Decramer M**. Respiratory function of the rib cage muscles. *Eur Respir J* 6: 722-728, 1993.
18. **Haslock I**. Ankylosing spondylitis. *Baillieres Clin Rheumatol* 7: 99-115, 1993.
19. **Ligier Y, Ratib O, Logean M, and Girard C**. Osiris: a medical image-manipulation system. *MD Comput* 11: 212-218, 1994.
20. **Morgan MD, Gourlay AR, Silver JR, Williams SJ, and Denison DM**. Contribution of the rib cage to breathing in tetraplegia. *Thorax* 40: 613-617, 1985.
21. **Mortola JP, and Sant'Ambrogio G**. Motion of the rib cage and the abdomen in tetraplegic patients. *Clin Sci Mol Med* 54: 25-32, 1978.
22. **Mueller G, Perret C, Hofer P, Berger M, Michel F, and Hopman M**. Computed tomography to assess respiratory mechanics in tetraplegic patients. In: *Chest* 2005, p. 388S.
23. **Roth EJ, Lu A, Primack S, Oken J, Nusshaum S, Berkowitz M, and Powley S**. Ventilatory function in cervical and high thoracic spinal cord injury. Relationship to level of injury and tone. *Am J Phys Med Rehab / Assoc Acad Physiatr* 76: 262-267, 1997.
24. **Sinderby C, Ingvarsson P, Sullivan L, Wickstrom I, and Lindstrom L**. The role of the diaphragm in trunk extension in tetraplegia. *Paraplegia* 30: 389-395, 1992.
25. **Spungen AM, Grimm DR, Schilero G, Lenner R, Oei E, Bauman WA, Almenoff PL, and Lesser M**. Relationship of respiratory symptoms with smoking status and pulmonary function in chronic spinal cord injury. *J Spinal Cord Med* 25: 23-27, 2002.
26. **Supinski GS, Levin S, and Kelsen SG**. Caffeine effect on respiratory muscle endurance and sense of effort during loaded breathing. *J Appl Physiol* 60: 2040-2047, 1986.
27. **Urmey W, Loring S, Mead J, Slutsky AS, Sarkarati M, Rossier A, and Brown R**. Upper and lower rib cage deformation during breathing in quadriplegics. *J Appl Physiol* 60: 618-622, 1986.



Chapter 9

General Discussion

The respiratory care of individuals with spinal cord injury (SCI) improved substantially over the last decades. Nevertheless, morbidity and mortality is still high in this population (15, 46) and there are various issues to be studied yet in order to further improve the respiratory care and the quality of life as well as to decrease respiratory complications, health care costs and mortality. In this thesis, three main aspects on respiration in SCI were assessed in seven specific studies. These three aspects were 'respiratory function after SCI', 'respiratory muscle endurance training in SCI' and 'rib cage mobility'. In the present chapter, the resulting data from these studies are put within the context of other data in the literature and are discussed in a comprehensive way. Further, the implications of the studies for future research that is striving to improve respiratory function of individuals with SCI are presented at the end of this chapter.

Respiratory function after SCI

The regression equations for lesion specific lung function and respiratory muscle pressure generating capacity presented in chapters 2 and 3 provide interesting information on influences of additional factors in SCI as well as changes over time early after injury.

In order to discuss the findings of former studies that tested respiratory function in SCI and to set them in relation to the results of the Dutch cohort study presented in this thesis, we created an overview of the largest studies published (2, 25, 26, 29, 37, 40) in combination with findings from our studies presented in chapters 2 and 3 (Table 1). This table shows relative lung function values and data representing respiratory muscle pressure generating capacity as percentage of able bodied predicted (4, 35) as well as group means of known determinants of respiratory function (i.e. time post injury and age). Since we found that completeness of the lesion significantly influences respiratory function (chapter 2), it is difficult to compare data of motor complete and incomplete individuals. Unfortunately not all of the larger studies distinguished between motor complete and incomplete subjects (26, 29, 40). Thus, where data of complete and incomplete subjects was reported separately, we only present the data of the motor complete subjects in Table 1. From this point of view, our own data can therefore mainly be compared to the studies of Almenoff et al., Roth et al. and Linn et al. (2, 25, 37). Only one study (37) tested subjects in the acute stage of SCI. These findings showed substantially lower lung function values than those we found one year after discharge from inpatient rehabilitation, confirming our findings of significantly increasing lung function during inpatient rehabilitation (chapter 3). Results of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) of the other two studies (2, 25) on individuals with motor complete SCI are lower than the values of our studies. These subjects were tested at longer time post injury and had a higher mean age, supporting our findings of negative regression coefficients for increasing age.

Table 1: Overview on findings of cohort studies that assessed respiratory function in subjects with SCI. Values are presented as group means and % of able bodied predicted.

Author year	Lesion level	[n]	Complete-ness	TPI [y]	Age [y]	FVC [%]	FEV_1 [%]	PEF [%]	Pi_{max} [%]	Pe_{max} [%]
Almenoff et al. 1995	C4 ↑	[7]	motor complete	15	49	34	35	34		
	C5-C8	[5]		17	38	57	66	63		
	T1-T7	[9]		33	60	84	95	85		
	T8-L3	[18]		22	54	87	86	85		
Roth et al. 1997	C4	[7]	motor complete	< 0.5	16-60	35	39			
	C5	[8]				39	43			
	C6	[18]				39	42			
	C7	[10]				45	48			
	T1	[5]				39	43			
Linn et al. 2000	C2-C5	[26]	motor complete	14	40	49	53	42		
	C6-C8	[9]				62	69	54		
	T1-T7	[28]				81	85	68		
	T8-L5	[13]				95	97	84		
Linn et al. 2001	C2-C5	[115]	mixed	15	44	53				
	C6-C8	[93]		15	44	69				
	T1-T6	[78]		18	46	79				
	T7-L5	[169]		17	47	88				
Spungen et al. 2002	TP nonS	[56]	mixed	17	49	57	60	47		
	TP S	[23]		12	43	63	59	49		
	PP nonS	[78]		22	54	84	86	78		
	PP S	[23]		15	46	77	73	71		
Mateus et al. 2007	C4-C5	[30]	mixed	2	34	49	58		50	19
	C6-C8	[22]		2.5	28	61	72		68	31
	T1-T6	[32]		2	27	70	77		84	38
	T7-L3	[47]		2	32	84	92		86	51
Chapter 2	TP	[30]	motor complete	2.4	29	74	76	54	56 [8]	14 [11]
	PP	[61]		1.8	39	89	87	69	82 [16]	36 [17]
Chapter 3	C3-C5	[14]	motor complete	2.5	36	63	64	46	53 [7]	16 [7]
	C6-C8	[16]		2.3	33	85	84	61	62 [4]	16 [4]
	T1-T6	[25]		1.9	43	84	82	66	71 [6]	28 [6]
	T7-T12	[36]		1.7	38	95	93	71	72 [10]	35 [11]

Abbreviations: n = number of subjects; TPI = time post injury; y = years; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 s; PEF = peak expiratory flow; Pi_{max} = maximal inspiratory muscle pressure; Pe_{max} = maximal expiratory muscle pressure; % = percent of able bodied predicted; C = cervical lesion; T = thoracic lesion; L = lumbar lesion; nonS = non smoker; S = smoker; TP = tetraplegics; PP = paraplegics. Concerning chapter 3: Note that only data from 1 year after discharge are presented in Table 1.

The study of Mateus et al. (29) is to our knowledge, the only one in the literature that provides values for Pi_{max} and Pe_{max} and the best one comparable to our studies concerning time post

injury. They assessed subjects with similar lesion level groups as we did in our longitudinal survey (chapter 3), but unfortunately they did not separate between motor complete and incomplete injuries. Since we found significant influences of completeness on Pi_{max} and Pe_{max}, the values found by Mateus et al. (29) can't be compared to the values of our study presented in chapter 2 of this thesis (Table 1). Nevertheless, even though our data and those of Mateus et al. (29) are based on a low number of subjects, both studies found that Pe_{max} is much more affected than Pi_{max} and that values increase with decreasing lesion level. Taking together all data on peak expiratory flow (PEF) shown in Table 1, which are based on a total of 477 subjects with SCI. Further support of our own findings is given by the groups of Almenoff, Linn and Spungen (2, 25, 40), showing that PEF values are more affected than FVC and FEV_1 (Table 1). Since expiratory muscle function, which can be measured by PEF and $Pe_{max,}$ is closely related to the ability to cough, a weak expiratory muscle function may influence the occurrence of respiratory tract infections substantially. Fugl-Meyer already reported in the mid-seventies that in patients with about 50% of the able bodied predicted Pe_{max}, PEF is sufficient for a productive cough (14). Although a reduction of 50% is substantial, all of our tested groups and most of the subjects tested by Mateus et al. (29) were below these 50% Pe_{max} (Table 1).

Coughing capacity which is related to the improvement of secretion clearance may be enhanced by various different methods described in the literature. Such methods consist of wearing an abdominal binder (5, 16), consulting the manual assistance of a therapist during coughing maneuvers (23), using electrical stimulation of the abdominal muscles (23) or in the spinal cord (9, 12) or training of in- or expiratory muscles (41). Since respiratory muscle training showed some evidence to increase respiratory muscle function and since this is the only method that is not directly dependent on technical equipment or a therapist during coughing, i.e. promising the highest independence for patients, we concentrated on respiratory muscle training in this thesis.

Respiratory muscle endurance training in SCI

Until now, most studies that investigated respiratory muscle training in individuals with SCI used inspiratory muscle strength training (11, 19, 21, 24, 27, 38, 44, 45). As early as the late nineties, Silva et al. (39) found that physical endurance exercise (arm cranking) improves ventilatory muscle endurance in paraplegic men, showing that the endurance component should be investigated as well. Nevertheless, until now influences of isolated respiratory muscle endurance training (normocapnic hyperpnoea) on respiratory and physical exercise performance have only been investigated in one very recent study with SCI subjects (42). This study was performed with a mixed SCI group of motor complete and incomplete para- and tetraplegic subjects between two and six month post injury. Nevertheless, results show positive first evidence of improved respiratory muscle strength and endurance and less frequent respiratory

complications (42). These results have to be confirmed for more consistent lesion groups as well as for individuals with acute and chronic SCI.

We showed that respiratory muscle endurance training can be performed by subjects with para- and tetraplegia, using normocapnic hyperpnoea training. The optimal training intensity is hereby lower for individuals with tetraplegia (40% maximal voluntary ventilation (MVV)) than for individuals with paraplegia (60% MVV) due to lower respiratory muscle endurance (chapter 4).

User specific objectives of normocapnic hyperpnoea training

While the main aim of normocapnic hyperpnoea training in healthy able bodied individuals constitutes an improvement of the physical exercise endurance performance, this may be similar in individuals with paraplegia, but it may be different in individuals with tetraplegia. Due to the very small amount of muscle mass that can be used for locomotion in individuals with tetraplegia (e.g. wheelchair propulsion or hand cycling), fatigue of arm and shoulder muscles may precede fatigue of respiratory muscles and thus normocapnic hyperpnoea training may not increase physical exercise performance to the same extent as it would in able bodied individuals (6, 7). Even if experiences from clinical practice support this hypothesis it should be tested in a controlled training study. The main aim of normocapnic hyperpnoea training in subjects with tetraplegia may be improvements in expiratory muscle pressure generating capacity and respiratory muscle endurance. Further goals may consist in improvements of respiratory muscle function in order to foster the coughing capacity and to reduce respiratory effort and probably also ventilator dependency during the night. Such effects may have substantial positive consequences on quality of life and hopefully also on reducing respiratory complications in individuals with tetraplegia. For individuals with C4 tetraplegia, normocapnic hyperpnoea training may be one of the only and most applicable endurance training methods that is expected to help boosting the confidence in a proper functioning of the own respiratory system.

Potential effects of normocapnic hyperpnoea training in individuals with SCI

Wheelchair racing athletes train their respiratory muscles during daily exercise practice. Nevertheless, results of the normocapnic hyperpnoea training study presented in chapter 5 showed that respiratory muscle endurance can further be improved. Physical endurance exercise performance and Pe_{max} showed a tendency to increase after normocapnic hyperpnoea training. The finding of an increased Pe_{max} in wheelchair racing athletes after 6 weeks of normocapnic hyperpnoea training represents the result with a high relevance for clinical practice and akinesic subjects with SCI. Since Pe_{max} is the most affected parameter in individuals with SCI (chapter 2 and 3), normocapnic hyperpnoea training may be an interesting option to increase expiratory muscle strength and hopefully decrease respiratory tract infections due to an increased coughing

capacity. The results of van Houtte et al. (42) confirm our findings of improved respiratory muscle strength and endurance after normocapnic hyperpnoea training in individuals with an acute SCI and even showed reductions in respiratory tract infections. This finding would of course be most important for subjects with tetraplegia which unfortunately were not evaluated separately in the study of van Houtte et al. (42). Due to the lower amount of active expiratory muscle mass in these individuals, effects of normocapnic hyperpnoea training may differ from results found in athletes with paraplegia.

Normocapnic hyperpnoea exercise as a mean to accelerate lactate removal?

A further potential effect of normocapnic hyperpnoea exercise is based on the fact that respiratory muscles mainly consist of type I muscle fibers which are able to use lactate as energy source (1, 8). Our results of normocapnic hyperpnoea exercise at different intensities (chapter 4) clearly showed that in subjects with paraplegia, lactate is used by respiratory muscles breathing at 20 and 40% of the individual MVV and in subjects with tetraplegia at 20% MVV. This shows that the reduced respiratory muscle mass of individuals with SCI is still able to metabolize lactate during normocapnic hyperpnoea, but also reflects the consequences on lactate removal due to differences in innervated respiratory muscle mass between individuals with para- and tetraplegia.

This effect may also be interesting for wheelchair racing athletes who often participate over various distances on the same competition day. Especially medium distance races over 400, 800 and 1500 m reveal high lactate concentrations in the working muscles (34). In order to give the arm muscles a break which may accelerate refill time of intramuscular carbohydrate storages but still improve lactate removal, low intensity normocapnic hyperpnoea exercise may theoretically be an interesting alternative to rest or low intensity wheelchair propulsion. Unfortunately, our results of the study reported in chapter 6 did not show faster lactate removal after low intensity normocapnic hyperpnoea exercise compared to passive and low intensity active recovery. Since this study was done in able bodied individuals, effects of normocapnic hyperpnoea on lactate removal may even be worse in individuals with SCI due to the lower amount of respiratory muscle mass that can be used for breathing exercise. As reported in chapter 6, the magnitude of the affected muscle mass seems to be critical to effective active recovery. Therefore we suggest that normocapnic hyperpnoea exercise should be used primarily in order to increase respiratory muscle and physical exercise performance in individuals with SCI.

Cardiovascular changes during normocapnic hyperpnoea training

Due to the frequently encountered akinesic lifestyle of individuals with SCI and limited possibilities to be active, secondary risk factors due to the degeneration of the cardio-pulmonary

system may cause severe complications and substantially decrease quality of life (31, 32). Normocapnic hyperpnoea training may have positive effects on the cardio-pulmonary function of subjects with SCI as well. Even though in able bodied individuals no effects from normocapnic hyperpnoea training on cardio-vascular responses to exercise were found (28), results of the study presented in chapter 4 potentially provide first indices of a possible cardio-pulmonary training effect from normocapnic hyperpnoea training in subjects with SCI. Subjects with paraplegia showed a larger increase of the systolic blood pressure than of the diastolic blood pressure during single sessions of normocapnic hyperpnoea exercise at an intensity of 60% MVV. This finding indicates that stroke volume may increase during normocapnic hyperpnoea training in subjects with paraplegia, which in turn may lead to a cardio-pulmonary training effect after regular normocapnic hyperpnoea training at 60% MVV over a period of several weeks. However, in this thesis we did not assess cardio-pulmonary changes after a period of normocapnic hyperpnoea training and therefore this assumption has yet to be tested in detail.

Should normocapnic hyperpnoea training prove to have positive effects not only on respiratory muscle endurance performance but also on the cardio-pulmonary system, normocapnic hyperpnoea training may become relevant for a much wider range of individuals with SCI. Haisma et al. (20) recently showed that physical fitness (i.e. peak power output and maximal oxygen uptake) was negatively associated with complications after discharge from inpatient rehabilitation in individuals with SCI. This study showed that bed rest time has to be kept as short as possible and high effort has to be put in improvements of physical fitness of individuals with SCI (20), in order to protect patients from getting into a downward spiral of low fitness and complications. Probably normocapnic hyperpnoea training can help to reach this goal at least in individuals with paraplegia. In subjects with tetraplegia, however, cardio-vascular effects of normocapnic hyperpnoea training may be lower or even absent due to the lack of activity of the sympathetic nervous system and a very low amount of respiratory muscle mass that can be activated during intensive breathing.

Moreover, shoulder problems are frequent in wheelchair users and often impair possibilities to additionally train the cardio-pulmonary system (10, 33). If normocapnic hyperpnoea training reveals positive effects on the cardio-pulmonary system in subjects with paraplegia, normocapnic hyperpnoea training may be a good alternative training option for individuals with shoulder problems. Therefore, studies on the effects of normocapnic hyperpnoea training on the cardio-pulmonary system of subjects with paraplegia should be conducted in the near future.

Rib cage mobility in able bodied and tetraplegic individuals

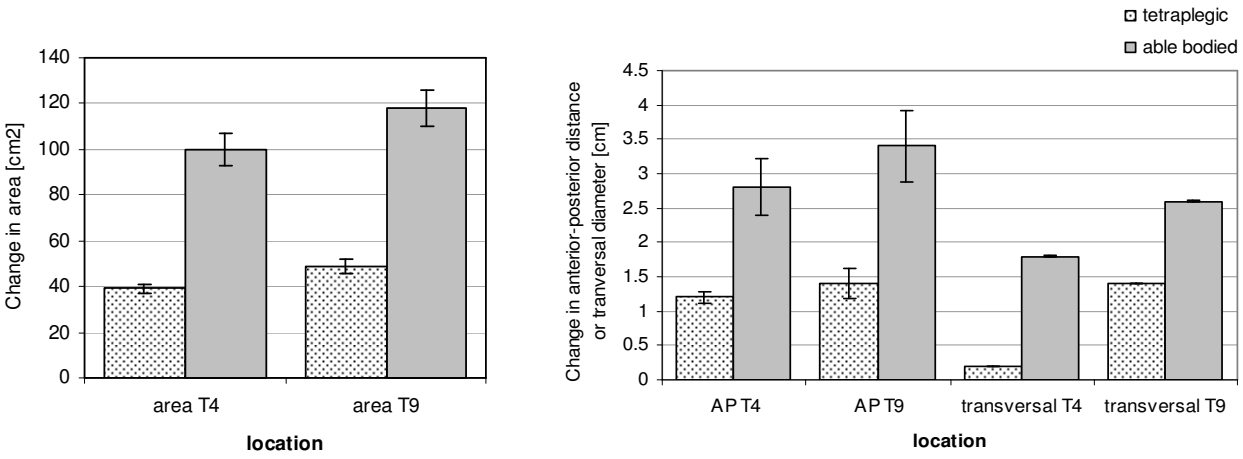
Rib cage mobility is substantially decreased in subjects with tetraplegia due to either respiratory muscle paralysis that changes and impairs respiratory mechanics, but also due to progressive stiffening of tissues and ankylosis in joints with increasing lesion duration (17). Stiffening of the

rib cage additionally increases the work put into breathing and may thus accelerate respiratory failure in individuals with tetraplegia (36). Thus, respiratory muscle training should also aim at improvements or at least maintenance of rib cage mobility. We developed a new method to measure rib cage mobility which showed very good reproducibility of measurements at maximal in- and expiration (chapter 7). We further compared diaphragmatic movement, intra-thoracic areas as well as anterior-posterior (AP) distances and transverse diameters of rib cage excursions from maximal breathing maneuvers between tetraplegic and gender-, age- and height- matched able bodied individuals (chapter 8).

Error vs. differences of rib cage mobility in tetraplegic and able bodied individuals

The added measurement errors of data at maximal in- and expiration plus their standard deviations (reported in chapter 7) have to be set in relation to changes between maximal in- and expiration in both groups of subjects (reported in chapter 8). Figures 1a and 1b show these total measurement errors of maximal breathing maneuvers including measurement errors' standard deviations in relation to absolute changes in areas and distances.

Figures 1a and 1b clearly show that added errors including their standard deviations (= error bars in Figures 1a and 1b) are still much smaller than differences in rib cage mobility between able bodied and tetraplegic individuals. Interestingly, areas and AP distances of rib cage excursions in individuals with tetraplegia are consistently around 40% of the ones from able bodied individuals. This raises the question whether both measures (areas and AP distances) are really necessary in order to report changes in rib cage mobility. For research purposes, due to the better reproducibility of intra-thoracic areas, both measures may produce better evidence, since changes due to interventions may be small. Nevertheless, for clinical use of this method a restriction on AP distances and transverse diameters should be discussed since this may bring forth important time saving and thus cost reduction of analysis. Nevertheless, to really answer this question, knowledge of changes due to interventions in individuals with tetraplegia is necessary.



Figures 1a and 1b: Changes in intra-costal area (Figure 1a) as well as anterior-posterior (AP) distance and transversal diameters (Figure 1b) from maximal inspiration to maximal expiration with indication of total measurement errors in tetraplegic and able bodied individuals. T4 = fourth thoracic vertebra; T9 = ninth thoracic vertebra. Note that errors of transversal diameters are too small to be shown (0.0004 to 0.008 cm)

Expected changes in rib cage mobility due to respiratory muscle training

Several studies found improvements in vital capacity (VC) after respiratory muscle training in subjects with tetraplegia (18, 22, 24, 38, 43, 47). Increases in VC may have effects on either rib cage or diaphragmatic excursions. In chapter 8 we showed that diaphragmatic function of individuals with motor complete tetraplegia below C5 is intact and the range of movement is not significantly lower than the one of able bodied individuals. Therefore, we can't expect any significant change in diaphragmatic volume displacement after respiratory muscle training. Thus, improvements in VC may primarily increase rib cage mobility. This would have effects on the intra-costal area and concomitantly also on AP distances and/or transverse diameters. In order to guess how much change in these parameters respiratory muscle training may induce, Table 2 presents an overview on the above mentioned studies that found improvements in VC after respiratory muscle training.

Table 2: Overview of respiratory muscle training studies that found improvements in vital capacity (VC)

Autor / year	**Groups/ subjects** [n]	**Lesion level complete-ness**	**Mean age** (range)	**TPI** [month]	**Training method and duration**	**Change in VC, if measured thoracic excursions**
Gounden et al.; 1990	2 / 40	C5-C8 complete-ness unknown	31 (16-64)	4-192 (acute and chronic)	EMT at 60% Pe_{max} initially increasing intensity 5 x 5-8 min/day, total at least 30 min/day 6 d/week for 8 weeks	Training Group: VC: 33% increase 1.47 to 1.97 l Control Group: no significant increases
Huldtgren et al.; 1980	2 / 35	C4-C8 complete	23 (16-69)	3-39	EMT + IMT 15 min/day for 6 weeks additionally: insuflating air to 100% TLC predicted with abdomen strapped	Training group: Significant increases in VC, Control group: no significant differences *no data of absolute values and changes (figures with individual values)*
Liaw et al.; 2000	2 / 20	C4 - C7	34 (16-52)	1-4.5	IMT with individually increasing resistance 15-20 min twice daily, 7 days/week, for 6 weeks	Training group: VC increased 66.7% from 1.2 to 2.0 l; FVC increased 50% from 1.2 to 1.8 l Control group: VC and FVC increased 26.7% from 1.5 to 1.9 l; Chest circumference only increased sign. in training group (+ 3.3cm at Xyphoid process; + 4.7cm at Umbilicus)
Rutchick et al.; 1998	1 / 10	C4-C7 (5 complete; 6 incom-plete)	36 (23-65)	24-228 (chronic)	IMT for 15 min twice daily; for 8 weeks	VC increased 8% from 2.9 to 3.1 l after training, FVC increased 11% from 2.81 to 3.07 l after training
Walker et al.; 1989	1 / 15	C4-C8 incomplete	? (17-33)	? (chronic)	3 to 5 x/week 15 min of incentive spirometry + 3x/week 30 min armcranking exercise; 7-12 week	VC increased 23.6 % from 2.5 to 3.26 l after training
Zupan et al.; 1997	1 / 13	C4-C7 (10 com-plete; 3 incomplete)	27 (17-46)	3-12	4 weeks IMT, 4 weeks EMT, 4 weeks no respiratory training in random order 7 different breathing exercises for 10 reps. each; twice a day 20-30 min; 6 days/week	after IMT: FVC increased 17% in supine position and 19% in sitting position after EMT: FVC increased 17% in supine position but showed no change in sitting position

Abbreviations: TPI = time post injury; C = cervical; EMT = expiratory muscle training; IMT = inspiratory muscle training; FVC = forced vital capacity

Changes in rib cage mobility after respiratory muscle training in individuals with tetraplegia may substantially be influenced by the time post injury. Due to progressive stiffening of the rib cage, respiratory muscle training may theoretically have more impact on rib cage mobility early after injury than in individuals with chronic tetraplegia. Nevertheless, since we found that lung volumes and respiratory muscle pressure generating capacity increased spontaneously during the first year post injury (chapter 3), improvements of the control group (Table 2) have to be subtracted from improvements of the training group for studies performed in individuals early after injury. In the study of Liaw et al. (24) for example, changes in VC that may be related to 6 weeks of inspiratory muscle training would then even be 40%, which is remarkable (see Table 2). Chest circumference measurements showed that in this study (24) individuals gained more volume in the lower part of the trunk, indicating that changes may predominantly come from improvements in diaphragmatic function. In our study all tested subjects were individuals with chronic tetraplegia (chapter 8) and we found no differences in diaphragmatic movements between able bodied individuals and subjects with tetraplegia. Therefore we can not make any conclusions about the potential to increase diaphragmatic function in individuals with acute tetraplegia at present.

Estenne and de Troyer (13) also reported that in tetraplegic individuals the general breathing pattern showed a greater expansion of the lower rather than the upper rib cage. They further found a more elliptical shape of the lower thoracic cage during inspiration. We also found a greater expansion of the lower than of the upper thoracic cage. The two studies in our overview (38, 43) (Table 2) that were conducted on individuals with chronic tetraplegia investigated quite different respiratory muscle training protocols. Probably as a cause of the additional arm cranking training in the study of Walker et al. (43) VC increases were much higher than in the other study where only inspiratory muscle strength training was performed.

Due to various differences in time post injury, training method and duration, completeness of injury and in some studies (24, 38, 43, 47) the lack of a control group makes it quite difficult to draw conclusions about the impact of respiratory muscle training on changes in chest wall mobility of tetraplegic individuals. Nevertheless, these six studies show evidence for potential increases in VC in individuals with acute and chronic tetraplegia after respiratory muscle training. Due to this positive first evidence, further studies should examine the effects of different respiratory muscle training methods in individuals with acute and chronic tetraplegia. Effects on thorax mobility, associated changes in respiratory function and, ideally, also possible influences on breathing capacity and concomitantly the rate and severance of respiratory complications should be addressed. To assess changes in thorax mobility our new method using CT (Chapter 7) should be used.

Some questions concerning this issue have to be answered by future studies; e.g. what type of training, how much change due to which respiratory muscle training can be expected and how much change would be advantageous for individuals with tetraplegia?

Implications of the studies and future directions for respiratory research in SCI

Lesion specific reference values for lung function and respiratory muscle pressure generating capacity

In chapter 2 and 3 we showed that respiratory function is affected to different extents in subjects with SCI, depending on lesion level and completeness. Therefore, lesion specific reference values are needed for lung function parameters and respiratory muscle pressure generating capacity. Such reference values would be very helpful for clinical practice in order to easily detect individuals with an increased risk at an early stage and to improve guidance for prevention as well as respiratory interventions. A meta-analysis of published studies that included a high number of subjects (25, 26, 29, 40), supplemented by further datasets of ample and uniformly distributed SCI cohorts would be necessary in order to build stable and lesion specific reference values for respiratory function parameters of individuals with SCI.

A further step would be to determine which respiratory function parameter correlates best with which pulmonary complication with respect to level and completeness of the lesion. Thresholds of increased risk for pulmonary complications should be defined for those respiratory function parameters with the highest correlations with pulmonary complications. The aim of such thresholds would be to get an objective measurement instrument for subjects with an increased risk. This could help to intensify respiratory care before complications occur and thus decrease respiratory complications and health care costs and increase quality of life and life expectancy, especially in subjects with tetraplegia.

Longitudinal trajectories and further influencing factors on respiratory function

The effects of aging on respiratory function in SCI may differ from those effects encountered in able bodied individuals. Therefore this aspect would be interesting to study in a long term follow-up study. Further, possible confounding factors such as age at injury, number, severity and frequency of respiratory tract infections, rehospitalisations, duration and intensity of physical and respiratory exercise training, artificial ventilation at night and various medications have not been identified yet and would be interesting factors to be studied in a long term follow-up as well.

Respiratory muscle training in individuals with tetraplegia

Respiratory muscle endurance training using normocapnic hyperpnoea showed increases in respiratory muscle endurance and expiratory muscle pressure generating capacity in paraplegic wheelchair racing athletes (chapter 5). These results are promising for individuals with tetraplegia. Thus, the effects of normocapnic hyperpnoea training on respiratory muscle endurance, pressure generating capacity and fatigue but also on rib cage mobility, the rate of respiratory complications, health care costs and quality of life in individuals with tetraplegia should be tested in a randomized controlled trial. Comparisons of normocapnic hyperpnoea training with other respiratory muscle training methods, e.g. training of in- or expiratory muscle pressure generating capacity or incentive spirometry, could be another important area of research. Concerning changes in rib cage mobility, comparisons of different respiratory muscle training methods would furthermore be instructive. Assuming that different respiratory muscle training methods exert varying effects on different respiratory muscle groups, the effects on rib cage mobility may differ as well. Using our method described in chapter 7, subjects of different respiratory muscle training groups could be measured before and after a training period in order to draw conclusions on changes in respiratory mechanics. This will hopefully help to find the individual optimal respiratory muscle training method for individuals according to their lesion level and respiratory problems.

Sleep disordered breathing is an additional further problem with a high incidence in individuals with tetraplegia. During the first year after acute tetraplegia, Berlowitz et al. (3) found an incidence of 60-83% of individuals with tetraplegia showing an apnea-hypopnea index of > 10 events/h. Wang et al. (44) provide first evidence that resistive inspiratory muscle endurance training may enhance sleep disordered breathing in individuals with tetraplegia. We hypothesize that normocapnic hyperpnoea training may have similar or even stronger effects on sleep disordered breathing than resistive inspiratory muscle endurance training, because sleep disordered breathing may depend more on endurance properties of respiratory muscles than on their maximal pressure generating capacity. Thus, effects of normocapnic hyperpnoea training on sleep disordered breathing in SCI patients with tetraplegia would be a further interesting issue for future research.

In summary, the overall goals of future research in the field of respiration in spinal cord injury should focus on finding means to effectively reduce respiratory complications and thus also reduce health care costs. This would in turn increase quality of life and life expectancy in individuals with SCI. Possible studies to achieve this goal thus should focus on:

i) Defining lesion specific reference values for lung function and respiratory muscle pressure generation including its most important influencing factors and thresholds for increased risk of respiratory complications.

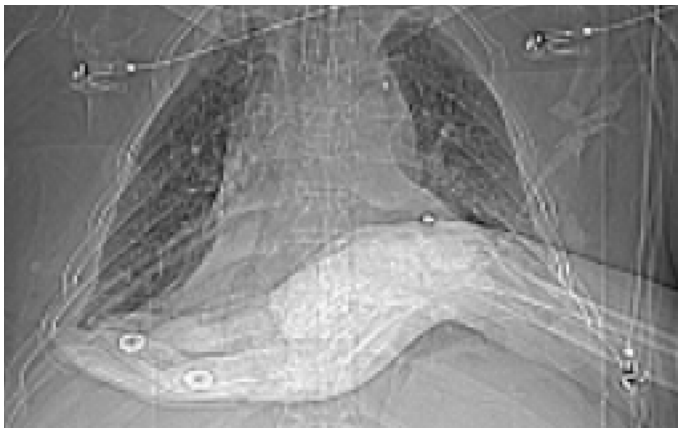
ii) Controlled respiratory muscle training studies in both subject with acute and chronic spinal cord injury. These studies should evaluate short and longterm effects of various respiratory muscle training methods on respiratory function and mechanics, rate and duration of respiratory complications, quality of life and sleep disordered breathing in individuals with SCI.

References

1. NHLBI Workshop summary. Respiratory muscle fatigue. Report of the Respiratory Muscle Fatigue Workshop Group. *Am Rev Respir Dis* 142: 474-480, 1990.
2. **Almenoff PL, Spungen AM, Lesser M, and Baumann WA**. Pulmonary function survey in spinal cord injury: influences of smoking and level and completeness of injury. *Lung* 173: 297-306, 1995.
3. **Berlowitz DJ, Brown DJ, Campbell DA, and Pierce RJ**. A longitudinal evaluation of sleep and breathing in the first year after cervical spinal cord injury. *Arch Phys Med Rehabil* 86: 1193-1199, 2005.
4. **Black LF, and Hyatt RE**. Maximal respiratory pressures: normal values and relationship to age and sex. *Am Rev Respir Dis* 99: 696-702, 1969.
5. **Boaventura CM, Gastaldi AC, Silveira JM, Santos PR, Guimaraes RC, and DeLima LC**. Effect of abdominal binder on the efficacy of respiratory muscles in seated and supine tetraplegic patients. *Physiotherapy* 89: 290-295, 2003.
6. **Boutellier U**. Respiratory muscle fitness and exercise endurance in healthy humans. *Med Sci Sports Exerc* 30: 1169-1172, 1998.
7. **Boutellier U, and Piwko P**. The respiratory system as an exercise limiting factor in normal sedentary subjects. *Eur J Appl Physiol Occup Physiol* 64: 145-152, 1992.
8. **Brooks GA, and Gaesser GA**. End points of lactate and glucose metabolism after exhausting exercise. *J Appl Physiol* 49: 1057-1069, 1980.
9. **Brown R, DiMarco AF, Hoit JD, and Garshick E**. Respiratory dysfunction and management in spinal cord injury. *Respir Care* 51: 853-868;discussion 869-870, 2006.
10. **Curtis KA, Drysdale GA, Lanza RD, Kolber M, Vitolo RS, and West R**. Shoulder pain in wheelchair users with tetraplegia and paraplegia. *Arch Phys Med Rehabil* 80: 453-457, 1999.
11. **Derrickson J, Cielsa N, Simpson N, and Imle PC**. A comparison of two breathing exercise programs for patients with quadriplegia. *Phys Ther* 72: 763-769, 1992.
12. **DiMarco AF, Kowalski KE, Geertman RT, and Hromyak DR**. Spinal cord stimulation: a new method to produce an effective cough in patients with spinal cord injury. *Am J Respir Crit Care Med* 173: 1386-1389, 2006.
13. **Estenne M, and De Troyer A**. Relationship between respiratory muscle electromyogram and rib cage motion in tetraplegia. *Am Rev Respir Dis* 132: 53-59, 1985.
14. **Fugl-Meyer AR**. The respiratory system. In: *Handbook of clinical Neurology*, edited by Vinken PJ, and Bruyn GW. New York: American Elsevier, 1976, p. 335-349.
15. **Garshick E, Kelley A, Cohen SA, Garrison A, Tun CG, Gagnon D, and Brown R**. A prospective assessment of mortality in chronic spinal cord injury. *Spinal Cord* 43: 408-416, 2005.
16. **Goldman JM, Rose LS, Williams SJ, Silver JR, and Denison DM**. Effect of abdominal binders on breathing in tetraplegic patients. *Thorax* 41: 940-945, 1986.
17. **Goldman JM, Williams SJ, and Denison DM**. The rib cage and abdominal components of respiratory system compliance in tetraplegic patients. *Eur Respir J* 1: 242-247, 1988.
18. **Gounden P**. Progressive resistive loading on accessory expiratory muscles in tetraplegia. *Fisioterapie* 46: 4-16, 1990.
19. **Gross D, Ladd HW, Riley EJ, Macklem PT, and Grassino A**. The effect of training on strength and endurance of the diaphragm in quadriplegia. *Am J Med* 68: 27-35, 1980.
20. **Haisma JA, Bussmann JB, Stam HJ, Sluis TA, Bergen MP, Post MW, Dallmeijer AJ, and van der Woude LH**. Physical fitness in people with a spinal cord injury: the association with complications and duration of rehabilitation. *Clin Rehabil* 21: 932-940, 2007.
21. **Hornstein S, and Ledsome JR**. Ventilatory muscle training in acute quadriplegia. *Physiotherapy Canada* 38: 145-149, 1986.

22. **Huldtgren AC, Fugl-Meyer AR, Jonasson E, and Bake B**. Ventilatory dysfunction and respiratory rehabilitation in post-traumatic quadriplegia. *Eur J Respir Dis* 61: 347-356, 1980.
23. **Jaeger RJ, Turba RM, Yarkony GM, and Roth EJ**. Cough in spinal cord injured patients: comparison of three methods to produce cough. *Arch Phys Med Rehabil* 74: 1358-1361, 1993.
24. **Liaw MY, Lin MC, Cheng PT, Wong MK, and Tang FT**. Resistive inspiratory muscle training: its effectiveness in patients with acute complete cervical cord injury. *Arch Phys Med Rehabil* 81: 752-756, 2000.
25. **Linn WS, Adkins RH, Gong H, Jr., and Waters RL**. Pulmonary function in chronic spinal cord injury: a cross-sectional survey of 222 southern California adult outpatients. *Arch Phys Med Rehabil* 81: 757-763, 2000.
26. **Linn WS, Spungen AM, Gong H, Adkins RH, Baumann WA, and Waters RL**. Forced vital capacity in two large outpatient populations with chronic spinal cord injury. *Spinal Cord* 39: 263-268, 2001.
27. **Loveridge B, Badour M, and Dubo H**. Ventilatory muscle endurance training in quadripegia: Effects on breathing pattern. *Paraplegia* 27: 329-339, 1989.
28. **Markov G, Spengler CM, Knopfli-Lenzin C, Stuessi C, and Boutellier U**. Respiratory muscle training increases cycling endurance without affecting cardiovascular responses to exercise. *Eur J Appl Physiol* 85: 233-239, 2001.
29. **Mateus SR, Beraldo PS, and Horan TA**. Maximal static mouth respiratory pressure in spinal cord injured patients: correlation with motor level. *Spinal Cord* 45: 569-575, 2007.
30. **Morgan MD, and De Troyer A**. The individuality of chest wall motion in tetraplegia. *Bull Eur Physiopathol Respir* 20: 547-552, 1984.
31. **Noreau L, Proulx P, Gagnon L, Drolet M, and Laramee MT**. Secondary impairments after spinal cord injury: a population-based study. *Am J Phys Med Rehabil* 79: 526-535, 2000.
32. **Noreau L, and Shephard RJ**. Spinal cord injury, exercise and quality of life. *Sports Med* 20: 226-250, 1995.
33. **Pentland WE, and Twomey LT**. Upper limb function in persons with long term paraplegia and implications for independence: Part I. *Paraplegia* 32: 211-218, 1994.
34. **Perret C, Mueller G, and Knecht H**. Influence of creatine supplementation on 800 m wheelchair performance: a pilot study. *Spinal Cord* 44: 275-279, 2006.
35. **Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, and Yernault JC**. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 16: 5-40, 1993.
36. **Rochester DF, and Arora NS**. Respiratory muscle failure. *Med Clin North Am* 67: 573-597, 1983.
37. **Roth EJ, Lu A, Primack S, Oken J, Nusshaum S, Berkowitz M, and Powley S**. Ventilatory function in cervical and high thoracic spinal cord injury. Relationship to level of injury and tone. *Am J Phys Med Rehabil* 76: 262-267, 1997.
38. **Rutchik A, Weissman AR, Almenoff PL, Spungen AM, Bauman WA, and Grimm DR**. Resistive inspiratory muscle training in subjects with chronic cervical spinal cord injury. *Arch Phys Med Rehabil* 79: 293-297, 1998.
39. **Silva AC, Neder JA, Chiurciu MV, Pasqualin DC, da Silva RC, Fernadez AC, Lauro FA, de Mello MT, and Tufik S**. Effect of aerobic training on ventilatory muscle endurance of spinal cord injured men. *Spinal Cord* 36: 240-245, 1998.
40. **Spungen AM, Grimm DR, Schilero G, Lenner R, Oei E, Bauman WA, Almenoff PL, and Lesser M**. Relationship of respiratory symptoms with smoking status and pulmonary function in chronic spinal cord injury. *J Spinal Cord Med* 25: 23-27, 2002.
41. **Van Houtte S, Vanlandewijck Y, and Gosselink R**. Respiratory muscle training in persons with spinal cord injury: A systematic review. *Respir Med* 100: 1886-1895, 2006.
42. **Van Houtte S, Vanlandewijck Y, Kiekens C, Spengler CM, and Gosselink R**. Patients with acute spinal cord injury benefit from normocapnic hyperpnoea training. *J Rehabil Med* 2007 (in Press); doi: 10.2340/16501977-0140.
43. **Walker J, Cooney M, and Norton S**. Improved pulmonary function in chronic quadriplegics after pulmonary therapy and arm ergometry. *Paraplegia* 27: 278-283, 1989.
44. **Wang TG, Wang YH, Tang FT, Lin KH, and Lien IN**. Resistive inspiratory muscle training in sleep-disordered breathing of traumatic tetraplegia. *Arch Phys Med Rehabil* 83: 491-496, 2002.

45. **Wanke T, Formanek D, Lahrmann H, Brath H, Wild M, Wagner C, and Zwick H**. Effects of combined inspiratory muscle and cycle ergometer training on exercise performance in patients with COPD. *Eur Respir J* 7: 2205-2211, 1994.
46. **Weaver FM, Smith B, Evans CT, Kurichi JE, Patel N, Kapur VK, and Burns SP**. Outcomes of outpatient visits for acute respiratory illness in veterans with spinal cord injuries and disorders. *Am J Phys Med Rehabil* 85: 718-726, 2006.
47. **Zupan A, Savrin R, Erjavec T, Kralj A, Karcnik T, Skorjanc T, Benko H, and Obreza P**. Effects of respiratory muscle training and electrical stimulation of abdominal muscle on respiratorycapabilities in tetraplegic patients. *Spinal Cord* 35: 540-545, 1997.



Summary

A spinal cord injury (SCI) causes lesion dependent impairments of respiratory muscles and thus may affect the respiratory system substantially. Respiratory complications increase with a higher lesion level and accordingly morbidity and mortality of individuals with SCI is substantially increased compared to the able bodied population (1, 4). In order to decrease respiratory complications, detailed knowledge of time-courses and lesion specific baseline characteristics of the respiratory function in subjects with SCI is needed. Thus, this thesis focused on baseline lung function and respiratory muscle pressure as well as on their time-courses during the first two years after injury, rib cage mobility, and respiratory muscle endurance training of different subgroups with SCI.

In **Chapter 1** a general overview of lesion specific impairments in SCI and its' epidemiology is shown. Then, the current knowledge of respiratory mechanics and different methods of respiratory muscle training in able bodied individuals and subjects with SCI are discussed and summarized. At the end of the chapter, the purposes of the studies presented in this thesis and the methods applied are presented.

The aim of the study presented in **Chapter 2** was to assess the influences of lesion and personal characteristics on respiratory function in subjects with SCI, one year after discharge from inpatient rehabilitation. We found that higher lesion levels are associated with lower lung function and especially lower respiratory muscle pressure generating capacity. Subjects with motor complete tetraplegia showed the highest impairments and expiratory muscle pressure was the most affected parameter in all subjects with SCI. Further, we present regression equations to estimate lesion specific lung function and respiratory muscle pressure for individuals with SCI, around two years post injury.

In **Chapter 3** we present trajectories of lung function and respiratory muscle pressure during and one year after inpatient rehabilitation for four different lesion level groups of subjects with motor complete SCI. We found that respiratory function improved during inpatient rehabilitation, but only forced vital capacity, forced expiratory volume in 1 s and maximal inspiratory muscle strength further improved during the first year after discharge from inpatient rehabilitation. The fact that maximal expiratory muscle pressure already decreased during the first year after inpatient rehabilitation shows that interventions to improve expiratory muscle function should be an important issue in respiratory care of subjects with SCI.

The aim of the study presented in **Chapter 4** was to adapt respiratory muscle endurance training using normocapnic hyperpnoea to the specific respiratory conditions of subjects with para- and tetraplegia, since this method was not used in subjects with SCI before. Thus, the aim was to find the level of ventilation that subjects with para-and tetraplegia can sustain for 10 to 20 minutes. These intensities may then be used as guidelines to implement respiratory muscle endurance training in subjects with SCI. In contrast to able bodied individuals who

sustain about 70% of their individual maximal voluntary ventilation (MVV) during 10 to 20 minutes, subjects with tetraplegia sustain only around 40% of their individual MVV during the target time and subjects with paraplegia are able to perform respiratory muscle endurance training at about 60% of their individual MVV for 10 to 20 minutes.

In **Chapter 5** we assessed the effects of respiratory muscle endurance training, using normocapnic hyperpnoea exercise, on exercise performance in wheelchair racing athletes with SCI. Effects of respiratory muscle endurance training on upper extremity exercise performance have not yet been investigated. They may differ from effects reported on leg endurance exercise performance in able bodied individuals, due to the concurrent use of upper extremity muscles for locomotion and respiration. We found significant increases in respiratory muscle endurance after six weeks of respiratory muscle endurance training performed five times a week during 30 min each. Due to high inter-individual differences and small group sizes, increases in expiratory muscle pressure and exercise performance (10 km time-trial) were only significant within the training group, but not between the training and the control group. Nevertheless, this study provides interesting preliminary results that show the potential effects of normopcapnic hyperpnoea training on respiratory muscle endurance, upper body exercise performance and expiratory muscle pressure in subjects with SCI.

High blood lactate levels are produced during anaerobic exercise intensities and blood lactate is used as energy source during low intensity exercise by type I muscle fibres. Normocapnic hyperpnoea exercise is performed by respiratory muscles which mainly contain type I fibres. Normocapnic hyperpnoea at low intensities may be advantageous as a recovery strategy in order to preserve energy sources of the limb muscles. The aim of the study presented in **Chapter 6** was to investigate the impact of low intensity normocapnic hyperpnoea on blood lactate disappearance after exhaustive arm exercise in comparison to passive and active recovery using the previously loaded muscle groups. The results showed that low intensity normocapnic hyperpnoea does not seem to enhance blood lactate disappearance after exhaustive arm exercise compared to passive or active recovery using the previously loaded muscle group. The magnitude of the involved muscle mass appears critical to effective active recovery.

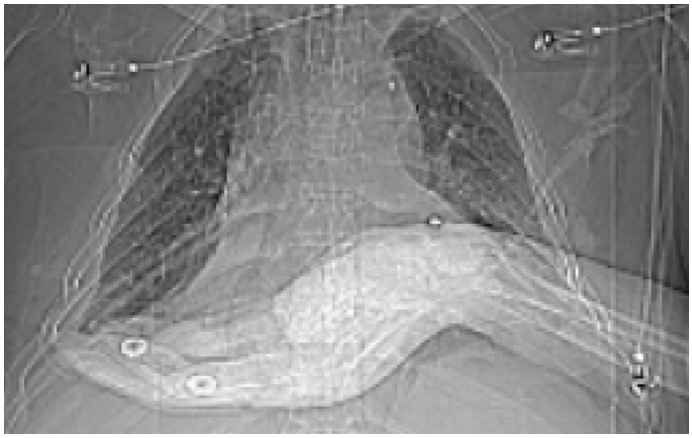
Stiffening of the thoracic cage decreases rib cage mobility and respiratory function, especially in subjects with chronic tetraplegia (2, 3). Thus, improvements in rib cage mobility should be a further aim of respiratory care in subjects with SCI. To determine which intervention should be used to achieve this goal, an easy to perform and highly reproducible measurement method of rib cage mobility should be available. In **Chapter 7** we present a new method to assess rib cage mobility in humans, using computed tomography. We showed that this method is highly reproducible in able bodied individuals and subjects with tetraplegia and thus useful for clinical practice.

In **Chapter 8** we assessed differences in rib cage mobility and diaphragmatic movements between able bodied individuals and subjects with chronic, motor complete tetraplegia, using the method described in chapter 7. Knowledge of such differences is important in order to quantify changes achieved in subjects with tetraplegia due to respiratory interventions, aiming at improvements in rib cage mobility. We found that rib cage mobility of individuals with chronic tetraplegia is reduced but not absent, whereas movement of the diaphragm is intact. Further, we present data of absolute differences in rib cage mobility and diaphragm movement between able bodied individuals and gender, age and height matched persons with chronic tetraplegia, including 95% confidence intervals.

In **Chapter 9** the current knowledge from former studies and data from this thesis on time-courses of respiratory function after injury and lesion specific impairments in respiratory function in SCI were discussed in a comprehensive way. Further, the potential of respiratory muscle endurance training to improve respiratory function in SCI was reviewed and discussed from previous studies and available data from this thesis. In addition, the issue of rib cage mobility and it's consequences on respiratory function were summarized and ideas to increase rib cage mobility were presented. Finally, we discussed some consequences and ideas for future research in order to improve respiratory function, decrease respiratory complications and health care costs and thus increase quality of life and life expectancy of subjects with spinal cord injury.

References

1. **Brown R, DiMarco AF, Hoit JD, and Garshick E**. Respiratory dysfunction and management in spinal cord injury. *Respir Care* 51: 853-868;discussion 869-870, 2006.
2. **Estenne M, and De Troyer A**. The effects of tetraplegia on chest wall statics. *Am Rev Respir Dis* 134: 121-124, 1986.
3. **Estenne M, Heilporn A, Delhez L, Yernault JC, and De Troyer A**. Chest wall stiffness in patients with chronic respiratory muscle weakness. *Am Rev Respir Dis* 128: 1002-1007, 1983.
4. **Zeilig G, Dolev M, Weingarden H, Blumen N, Shemesh Y, and Ohry A**. Long-term morbidity and mortality after spinal cord injury: 50 years of follow-up. *Spinal Cord* 38: 563-566, 2000.



Samenvatting

Een gevolg van een dwarslaesie is dat er, afhankelijk van de hoogte van de laesie, uitval van de ademhalingsspieren optreedt. Deze uitval van ademhalingsspieren heeft gevolgen voor het functioneren van het ademhalingssysteem als geheel. Hoe hoger het niveau van de dwarslaesie, hoe groter de kans op complicaties van het ademhalingssysteem met als gevolg een hogere morbiditeit en mortaliteit in vergelijking tot gezonde personen (1, 4). Om het risico op complicaties te verminderen, is gedetailleerde kennis nodig van onder andere specifieke laesieniveau afhankelijke kenmerken en het beloop over tijd van deze kenmerken. Dit proefschrift concentreert zich op de basale longfunctie, de kracht en het uithoudingsvermogen van de ademhalingsspieren, als ook de beweeglijkheid van de thorax in de verschillende subgroepen van personen met een dwarslaesie. Daarnaast wordt het effect van training van het uithoudingsvermogen van de ademhalingsspieren besproken.

In **Hoofdstuk 1** wordt de epidemiologie van een dwarslaesie getoond en een algemeen overzicht gegeven van de gevolgen van een dwarslaesie. Vervolgens wordt de huidige kennis omtrent de werking van de ademhalingsspieren en het effect van verschillende trainingsvormen in de gezonde populatie en in personen met een dwarslaesie samengevat en besproken. Dit hoofdstuk eindigt met het benoemen van de doelen van de verschillende studies die gedaan werden voor dit proefschrift en met presentatie van de gebruikte methodiek.

Het doel van de studie, zoals in **Hoofdstuk 2** besproken, was het vaststellen van de invloeden van laesiespecifieke en persoonsspecifieke kenmerken op de ademhalingsfunctie in personen met een dwarslaesie, één jaar na ontslag uit het revalidatiecentrum. Er is een verband gevonden tussen laesieniveau, longfunctie en kracht van de ademhalingsspieren. Een hoger laesieniveau is geassocieerd met een verminderde longfunctie en een verminderd vermogen van de ademhalingsspieren om kracht te genereren. Personen met een complete tetraplegie hebben de meest aangedane longfunctie en de minste kracht van ademhalingsspieren. Daarnaast worden in dit hoofdstuk regressievergelijkingen gepresenteerd voor het schatten van de longfunctie en de kracht van de ademhalingsspieren voor personen met een dwarslaesie, 2 jaar na het ontstaan van de laesie.

In **Hoofdstuk 3** wordt het beloop van longfunctie en kracht van de ademhalingsspieren tijdens en 1 jaar na de klinische revalidatie besproken. Vier, op laesieniveau ingedeelde, groepen met een motorisch complete dwarslaesie zijn geanalyseerd. Gegevens uit de longitudinale studie lieten zien dat de ademhalingsfunctie tijdens klinische revalidatie verbeterde, maar dat in het eerste jaar na klinische revalidatie alleen geforceerde vitale capaciteit, geforceerde expiratoire volume in 1 seconde en maximale in- of uitademingskracht nog verder verbeterden. De maximale in- en uitademingskracht zijn vermindert in het eerste jaar na klinische revalidatie. Dit gegeven leidt tot de conclusie dat interventies nodig zijn om de kracht van de uitademingsspieren functie te verbeteren. Dit is een belangrijk aandachtspunt in de zorg voor personen met een dwarslaesie.

Het doel van de studie, zoals gepresenteerd in **Hoofdstuk 4**, is het ontwikkelen van het uithoudingsvermogen van de ademhalingsspieren op basis van *normaocapnic hyperpnoe*, voor personen met een dwarslaesie. Aangezien dit soort training niet eerder is toegepast bij dwarslaesiepatiënten, is deze training aangepast aan de specifieke kenmerken van deze groep. De trainingsintensiteit is zo ontwikkeld dat personen met een dwarslaesie deze training 10 tot 20 minuten konden volhouden. Deze intensiteit is als richtlijn gebruikt voor training van nieuwe dwarslaesiepatiënten. In vergelijking met de gezonde populatie, die ongeveer 70% van hun maximale vrijwillige ventilatie (MVV) gebruiken binnen de 10 tot 20 minuten durende trainingstijd, gebruiken personen met een paraplegie 60% en personen met een tetraplegie maar 40% van hun MVV.

In **Hoofdstuk 5** beschrijven we de uitkomsten van een onderzoek naar training van het uithoudingsvermogen van de ademhalingsspieren, door middel van *normocapnic hyperpnoe* oefeningen, op de fysieke prestatie van rolstoelatleten met een dwarslaesie. Er is nog geen eerder onderzoek gedaan naar het effect van training van de ademhalingsspieren op de prestatie geleverd door de bovenste extremiteit. Onze hypothese was dat bij gezonde proefpersonen, ademhalingsspiertraining een ander effect zou hebben op inspanning geleverd door de bovenste extremiteiten dan op inspanning geleverd door de onderste extermiteiten. Het idee hierachter is dat dezelfde spiergroepen gebruikt worden voor ademhalen en het gebruik van de bovenste extremiteiten. In deze studie vonden we na 6 weken training van de ademhalingsspieren (5 maal per week 30 min) een significante toename van het uithoudingsvermogen van deze ademhalingsspieren. Ook vonden we een significant verschil tussen de kracht van de uitademingsspieren en de prestatie op een 10 kilometer tijdrit in de trainingsgroep. Deze uitkomsten zijn niet significant verschillend tussen de controlegroep en de trainingsgroep, waarschijnlijk ten gevolge van de kleine groepsgrootte en de grote verschillen tussen de proefpersonen. De resultaten van deze studie tonen wel aan dat er een potentieel effect is van *normocapnic hyperpnoe* training op het uithoudingsvermogen van de ademhalingsspieren, de prestatie van de bovenste extremiteit en de kracht van de uitademingsspieren in personen met een dwarslaesie.

Tijdens anaerobe inspanning wordt een verhoogd gehalte van bloedlactaat gevonden. Bloedlactaat wordt gebruikt als een bron van energie tijdens inspanning met lage intensiteit door type 1 spiervezels. *Normaocapnic hyperpnoe* traint voornamelijk de ademhalingsspieren die uit dit type 1 vezels bestaan en wordt op lage intensiteit verricht. *Normaocapnic hyperpnoe* heeft daardoor het voordeel dat er energie gespaard kan worden voor beenspieren. Het doel van de studie beschreven in **Hoofdstuk 6**, was het onderzoeken van de impact van *normocapnic hyperpnoe* op afname van bloedlactaat niveau na arm-inspanning in vergelijking tot de afname bij passief en actief herstel van de eerder belaste spiergroepen. Onze resultaten tonen aan dat *normocapnic hyperpnoe* de afname van

bloedlactaat na arm-inspanning niet verhoogd. Wel werd een verband aangetoond tussen de hoeveelheid spiermassa en het effectief actief herstel.

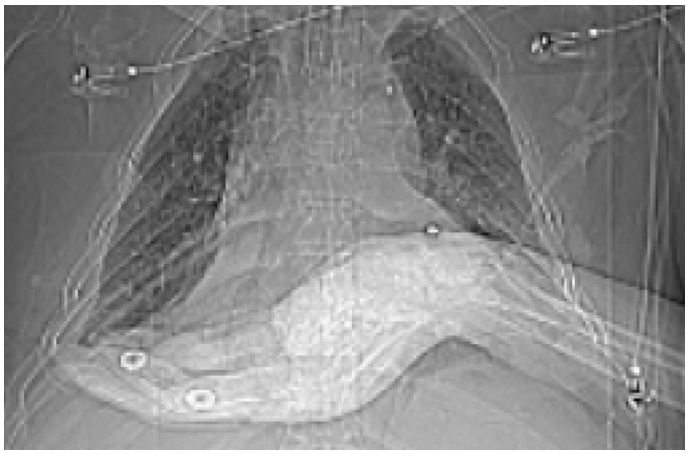
Stijfheid van de borstkas vermindert de beweeglijkheid van de borstkas en daardoor ook de ademhalingsfunctie, in het bijzonder in personen met een chronische tetraplegie (2, 3). Verbetering van de mobiliteit van de borstkas zou een aandachtspunt moeten zijn in de zorg van personen met een dwarslaesie. Om de beweeglijkheid van de borstkas in de klinische praktijk te kunnen meten en te bepalen welke interventie er plaats zou moeten vinden is een gemakkelijk uit te voeren en reproduceerbare meetmethode nodig. In **Hoofdstuk 7** presenteren we een nieuwe methode om de mobiliteit van de borstkas te bepalen door gebruik van computer tomografie (CT). We tonen aan dat deze methode reproduceerbaar is bij gezonde personen en bij personen met een tetraplegie en bruikbaar is in de praktijk.

Hoofdstuk 8 richt zich op het beschrijven van de verschillen in beweeglijkheid van de borstkas in gezonde personen en personen met een complete tetraplegie. Hiertoe hebben we de methode zoals in hoofdstuk 7 beschreven gebruikt. Het is van belang de verschillen in de mobiliteit van de borstkas te weten tussen gezonde proefpersonen en personen met een tetraplegie om de veranderingen in de beweeglijkheid van de borstkas, die gemeten werd in personen met een tetraplegie door interventies te kunnen kwantificeren. We vonden dat in personen met een complete tetraplegie de mobiliteit van de borstkas verminderd is, maar niet geheel afwezig. De verklaring die we hiervoor geven is dat de werking van het diafragma intact is. In dit hoofdstuk presenteren we verder de data betreffende de verschillen in de beweeglijkheid van de borstkas tussen gezonde proefpersonen en op geslacht, leeftijd en lichaamslengte gematchte personen met een tetraplegie.

In **Hoofdstuk 9** bediscussiëren we de tot nu toe beschreven kennis betreffende beloop in ademhalingsfunctie, en laesie specifieke beperkingen in ademhalingsfunctie in personen met een dwarslaesie zoals beschreven in de literatuur en de door ons gevonden resultaten. Ook wordt het potentiële effect van ademhalingsspier-training door middel van *normocapnic hyperpnoe* training, zoals gevonden in onze studie, besproken aan de hand van eerder gevonden studieresultaten. Vervolgens bespreken we de resultaten van onze studie betreffende de beweeglijkheid van de borstkas en de gevolgen van een verminderde beweeglijkheid van de borstkas in personen met een dwarslaesie en doen we een voorstel om de beweeglijkheid van de borstkas te verbeteren. Ten slotte beschrijven we de gevolgen van een verminderde ademhalingsfunctie in personen met een dwarslaesie en doen voorstellen om deze te verbeteren. Deze voorstellen hebben een potentieel tot een vermindering van complicaties van de ademhalingswegen, zoals infecties. Het gevolg hiervan is een vermindering van kosten voor de gezondheidszorg en een verbeterde kwaliteit van leven in personen met een dwarslaesie.

Referenties

1. **Brown R, DiMarco AF, Hoit JD, and Garshick E**. Respiratory dysfunction and management in spinal cord injury. *Respir Care* 51: 853-868;discussion 869-870, 2006.
2. **Estenne M, and De Troyer A**. The effects of tetraplegia on chest wall statics. *The American review of respiratory disease* 134: 121-124, 1986.
3. **Estenne M, Heilporn A, Delhez L, Yernault JC, and De Troyer A**. Chest wall stiffness in patients with chronic respiratory muscle weakness. *The American review of respiratory disease* 128: 1002-1007, 1983.
4. **Zeilig G, Dolev M, Weingarden H, Blumen N, Shemesh Y, and Ohry A**. Long-term morbidity and mortality after spinal cord injury: 50 years of follow-up. *Spinal Cord* 38: 563-566, 2000.



Zusammenfassung

Eine Querschnittlähmung führt oft zu Beeinträchtigungen der Atmungsmuskulatur und dies wirkt sich auf das gesamte respiratorische System aus. Dabei gilt: Je höher die Lähmung, desto grösser die Beeinträchtigungen der Atmungsmuskulatur und die Gefahr von Atemwegskomplikationen. Infolgedessen sind die Morbidität und Mortalität von querschnittgelähmten Personen im Vergleich zu Fussgängern substantiell erhöht (1, 4). Um das Auftreten von Atemwegskomplikationen in Zukunft zu vermindern, ist es notwendig den Verlauf sowie läsionsabhängige Einschränkungen der Lungenfunktion von Patienten mit Querschnittlähmung genau zu kennen. Daher sind die Hauptthemen dieser Dissertation dem Verlauf der Lungenfunktion und Atmungsmuskelkraft, den Einschränkungen der Thoraxmobilität sowie dem Atmungsausdauertraining mittels normokapnischer Hyperpnoe gewidmet.

In **Kapitel 1** wird ein genereller Überblick zum Thema Querschnittlähmung, deren Epidemiologie und läsionsabhängiger Funktionseinschränkungen vermittelt. Anschliessend wird das heutige Wissen der Bereiche Atemmechanik sowie verschiedene Atmungstrainingsmethoden bei Fussgängern und querschnittgelähmten Personen diskutiert und zusammengefasst. Am Schluss dieses Kapitels werden die Fragestellungen der einzelnen Kapitel dieser Dissertation vorgestellt sowie die verwendeten Methoden erklärt.

In **Kapitel 2** wird eine Studie präsentiert, deren Ziel es war den Einfluss der Lähmungshöhe sowie persönlicher Faktoren auf die Atmungsfunktion bei Personen ein Jahr nach Ende der Erstrehabilitation zu bestimmen. Dabei haben wir herausgefunden dass eine höhere Lähmungshöhe eine schlechtere Lungenfunktion und vor allem eine tiefere Atmungsmuskelkraft zur Folge hat. Patienten mit motorisch kompletter Tetraplegie waren die am stärksten betroffene Patientengruppe und die maximale Kraft der Ausatmungsmuskulatur war der am meisten beeinträchtigte Parameter. Zudem präsentieren wir in diesem Kapitel Regressionsgleichungen um läsionsspezifische Lungenfunktions- und Atmungs-muskelkraftwerte für querschnittgelähmte Personen ein Jahr nach Ende der Erstrehabilitation zu berechnen.

In **Kapitel 3** werden die Verläufe der Lungenfunktion und Atmungsmuskelkraft während der Erstrehabilitation sowie 1 Jahr danach bei verschiedenen ‚Läsionshöhen-Gruppen' motorisch komplett gelähmter Patienten untersucht. Dabei fanden wir heraus, dass sich die Lungenfunktion während der Erstrehabilitation signifikant verbessert, danach jedoch nur die forcierte Vitalkapazität, die Erstsekundenkapazität sowie die maximale inspiratorische Kraft nach Ende der Erstrehabilitation noch weiter ansteigen. Die Tatsache, dass die maximal Kraft der Ausatmungsmuskulatur bereits während der Erstrehabilitation wieder abnimmt, zeigt, dass Interventionen zur Funktionsverbesserung der Ausatmungsmuskulatur ein wichtiger Faktor des Atemwegsmanagements bei Querschnittlähmung sein sollten.

Das Ziel der Studie, die in **Kapitel 4** präsentiert wird, war das Atmungsausdauertraining mittels normokapnischer Hyperpnoe auf die speziellen Voraussetzungen von Personen mit Para- und Tetraplegie zu adaptieren. Bis dato wurde diese Methode noch in keiner wissenschaftlichen Publikation mit querschnittgelähmten Patienten beschrieben. Daher war das Ziel unserer Studie eine Trainingsintensität zu finden, bei der Para- und Tetraplegiker im Stande sind zwischen 10 und 20 Minuten zu trainieren. Diese Intensitäten sollen dann gebraucht werden um Atmungsausdauertraining auch bei Patienten mit Para- und Tetraplegie in der Praxis anzuwenden. Im Vergleich zu Fussgängern, die eine Intensität von 70% des Atemgrenzwertes ca. 10-20 Minuten ausüben können, fanden wir tiefere Intensitäten für querschnittgelähmte Personen. Tetraplegiker können bei nur etwa 40% des individuellen Atemgrenzwertes 10-20 Minuten atmen, während Paraplegiker dies bei ca. 60% des individuellen Atemgrenzwertes gelingt.

In **Kapitel 5** haben wir die Effekte eines Atmungsausdauertrainings mittels normokapnischer Hyperpnoe auf die Ausdauerleistungsfähigkeit von Rennrollstuhlathleten untersucht. Die Effekte eines Atmungsausdauertrainings auf die körperliche Leistungsfähigkeit der oberen Extremitäten wurden bis dato nicht untersucht; diese könnten sich von Effekten auf die unteren Extremitäten unterscheiden, da die oberen Extremitäten gleichzeitig zum atmen und zur Fortbewegung gebraucht werden. Wir fanden signifikante Verbesserungen der Atmungsausdauer nach sechs Wochen Atmungsausdauertraining, das fünf Mal wöchentlich während je 30 Minuten absolviert wurde. Wegen grosser inter-individueller Unterschiede und kleinen Gruppengrössen waren die Verbesserungen der Maximalkraft der Ausatmungsmuskulatur sowie die Verbesserungen im 10 km Zeitfahren nur innerhalb der Trainingsgruppe, jedoch nicht zwischen Trainings- und Kontrollgruppe signifikant. Nichtsdestotrotz zeigt diese Studie interessante erste Resultate, nämlich die potentiell positiven Effekte eines Atmungsausdauertrainings bei Patienten mit Querschnittlähmung auf die Atmungsmuskelausdauer, die Ausatmungskraft und die Ausdauerleistungsfähigkeit der oberen Extremitäten.

Während hochintensiven körperlichen Anstrengungen entstehen hohe Blutlaktatkonzentrationen. Laktat kann aber bei sportlichen Aktivitäten tiefer Intensität von den Typ I Muskelfasern wieder als Energiequelle genutzt werden. Die Atmungsmuskulatur besteht mehrheitlich aus Typ I Fasern. Normokapnische Hyperpnoe kann auch bei tiefen Intensitäten durchgeführt werden und dadurch hohe Blutlaktatkonzentrationen möglicherweise wesentlich senken. Daher könnte normokapnische Hyperpnoe eine vorteilhafte Erholungsmethode sein, da die intramuskulären Glykogenspeicher der Arbeitsmuskulatur (Arme oder Beine) geschont oder sogar schneller wieder aufgefüllt werden könnten. Das Ziel der Studie, die in **Kapitel 6** präsentiert wird, war daher, den Einfluss von normokapnischer Hyperpnoe auf den Abbau der Blutlaktatkonzentration nach intensiver Armarbeit im Vergleich zu passiver und aktiver Erholung der zuvor belasteten Muskulatur zu

untersuchen. Die Resultate haben gezeigt, dass normokapnische Hyperpnoe tiefer Intensität die Abbaurate der Blutlaktatkonzentration nach intensiver Armarbeit im Vergleich zu passiver und aktiver Erholung der belasteten Muskulatur nicht zu erhöhen vermag. Die zur Erholung eingesetzte Muskelmasse scheint entscheidend zu sein für eine effektive aktive Erholung.

Das progressive Versteifen des Thorax, welches vor allem bei Tetraplegikern häufig ist, vermindert dessen Mobilität und in der Folge auch die Funktion der Atmungsmuskulatur (2, 3). Deshalb sollten Verbesserungen der Thoraxmobilität ein weiteres Ziel der Atemtherapie bei Querschnittlähmung sein. Um überhaupt bestimmen zu können, welche Intervention zu den grössten Verbesserungen der Thoraxmobilität führt, ist eine einfache und genaue Messmethode der Thoraxmobilität nötig. Daher präsentieren wir in **Kapitel 7** eine neue Methode um die Thoraxmobilität mittels Computertomographie zu messen. Wir konnten zeigen, dass diese Methode sowohl bei Fussgängern als auch bei Patienten mit chronischer Tetraplegie sehr gut reproduzierbare Resultate erzeugt und daher in der Praxis einsetzbar ist.

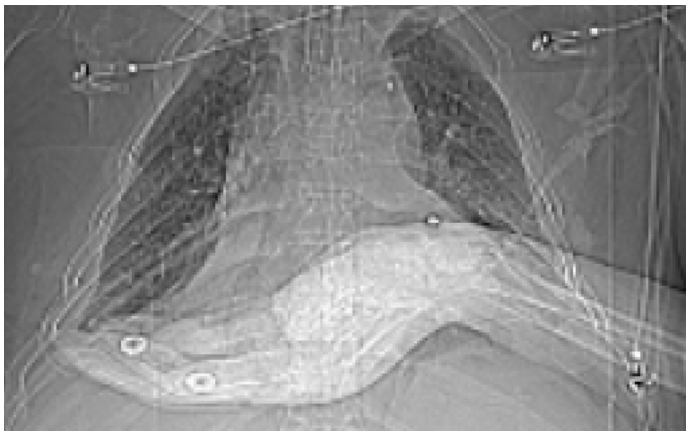
In **Kapitel 8** haben wir die Unterschiede der Thoraxmobilität von Fussgängern und motorisch kompletten, chronischen Tetraplegikern mittels der in Kapitel 6 beschriebenen Methode untersucht. Die genaue Kenntnis solcher Unterschiede ist wichtig, um Veränderungen der Thoraxmobilität über die Zeit hinweg oder nach bestimmten Interventionen zu quantifizieren. Wir fanden heraus, dass die Thoraxmobilität bei chronischen Tetraplegikern zwar reduziert, aber doch vorhanden ist und dass die Diaphragmamobilität noch vollständig intakt ist. Weiter präsentieren wir Daten, inklusive deren 95% Konfidenz Intervalle, der absoluten Unterschiede der Thoraxmobilität von Fussgängern und Tetraplegikern.

In **Kapitel 9** werden das derzeitige Wissen aus der Literatur und die Daten dieser Dissertation in den Bereichen ‘Verläufe der Lungenfunktion nach Querschnittlähmung’ und ‚Läsionsspezifische Einschränkungen der Lungenfunktion’ übergreifend diskutiert. Weiter wird das Potential von Atmungsausdauertraining im Bereich der Querschnittlähmung in Verbindung mit Resultaten anderer Atmungstrainingsstudien diskutiert. Zum Thema der Thoraxmobilität und deren Konsequenzen auf die Atmung zusammengefasst und Ideen zur Verbesserung der Thoraxmobilität werden diskutiert. Schliesslich werden einige Konsequenzen, die aus den in dieser Dissertation präsentierten Studien hervorgehen, diskutiert und Vorschläge für weiterführende Studien präsentiert. Ziele dieser weiterführenden Studien sollten die Verminderung von Atemwegskomplikationen sein und damit verbundene tiefere Gesundheitskosten sowie eine verbesserte Lebensqualität querschnittgelähmter Personen.

Referenzen

1. **Brown R, DiMarco AF, Hoit JD, and Garshick E**. Respiratory dysfunction and management in spinal cord injury. *Respir Care* 51: 853-868;discussion 869-870, 2006.

2. **Estenne M, and De Troyer A**. The effects of tetraplegia on chest wall statics. *Am Rev Respir Dis* 134: 121-124, 1986.
3. **Estenne M, Heilporn A, Delhez L, Yernault JC, and De Troyer A**. Chest wall stiffness in patients with chronic respiratory muscle weakness. *Am Rev Respir Dis* 128: 1002-1007, 1983.
4. **Zeilig G, Dolev M, Weingarden H, Blumen N, Shemesh Y, and Ohry A**. Long-term morbidity and mortality after spinal cord injury: 50 years of follow-up. *Spinal Cord* 38: 563-566, 2000.



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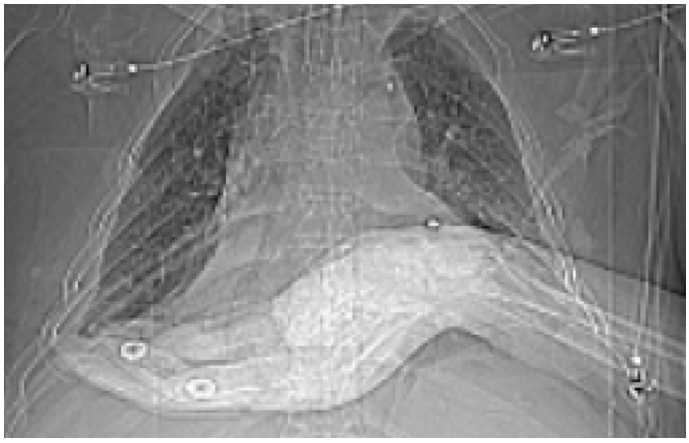


Publications

1. Knechtle B, Müller G. Ernährung bei einem Extremausdauerwettkampf. (2002) *Dt Zschr Sportmed* 53(2):54-57

2. Knechtle B, Hardegger K, Muller G, Odermatt P, Eser P, Knecht H. Evaluation of sprint exercise testing protocols in wheelchair athletes. (2003) *Spinal Cord* 41:182-186

3. Twerenbold R, Knechtle B, Kakebeeke TH, Eser P; Muller G, Von Arx P, Knecht H. Effects of different sodium concentrations in fluid replacement during prolonged exercise. (2003) *Br J Sports Med* 37:300-303

4. Knechtle B, Muller G, Willmann F, Eser P, Knecht H. Comparison of fat oxidation in arm cranking in spinal cord-injured people versus ergometry in cyclists. (2003) *Eur J Appl Physiol* 90:614-619

5. Knechtle B, Muller G, Willmann F, Kotteck K, Eser P, Knecht H. Fat oxidation in men and women endurance athletes in running and cycling. (2004) *Int J Sports Med* 25:38-44

6. Knechtle B, Muller G, Willmann F, Eser P, Knecht H. Fat oxidation at different intensities in wheelchair racing. (2004) *Spinal Cord* 42:24-28

7. Knechtle B, Muller G, Knecht H. Optimal exercise intensities for fat metabolism in handbike cycling and cycling. (2004) *Spinal Cord* 42:564-572

8. Muller G, Odermatt P, Perret C. A new test to improve the training quality of wheelchair racing athletes. (2004) *Spinal Cord* 42: 585-590

9. Perret C, Mueller G. Validation of a new portable ergospirometric device (Oxycon mobile) during exercise. (2006) *Int J Sports Med* 27(5):363-367

10. Perret C, Mueller G, Knecht H. Influence of creatine supplementation on 800m wheelchair performance: a pilot study. (2006) *Spinal Cord* 44(5):275-279

11. Mueller G, Perret C, Spengler CM. Optimal intensity for respiratory muscle endurance training in patients with spinal cord injury. (2006) *J Rehabil Med* 38(6):381-386 *(Chapter 4)*

12. Mueller G, de Groot S, van der Woude L, Hopman M.T.E. Time-courses of lung function and respiratory muscle pressure generating capacity after spinal cord injury: A prospective cohort study. (2008) *J Rehabil Med* 40:269-276 *(Chapter 3)*

13. Mueller G, Perret C, Hopman M.T.E. Effects of respiratory muscle endurance training on wheelchair racing performance in spinal cord injured athletes: a pilot study. (2008) *Clin J Sport Med; 18:85-88 (Chapter 5)*

14. Perret C, Mueller G. Impact of low intensity isocapnic hyperpnoea on blood lactate disappearance after exhaustive arm exercise. (2007) *Br J Sports Med 41:588-591 (Chapter 6)*
15. Strupler M, Mueller G and Perret C: Heart rate based lactate minimum test - a reproducible method? (2008) *Br J Sport Med (in Press)*

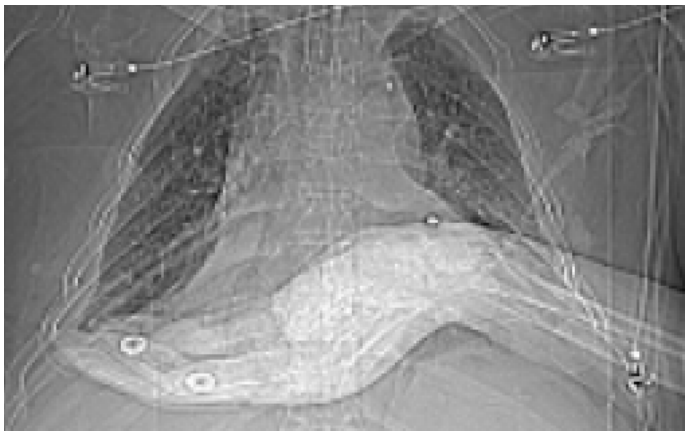
Submitted for publication 2008 (this thesis)

16. Mueller G, de Groot S, van der Woude L, Hopman M.T.E. Determinants and lesion-dependent impairments of respiratory function in spinal cord injury. *(Chapter 2)*
17. Mueller G, Perret C, Hofer P.J, Michel F, Berger M, Hopman M.T.E. Reproducibility of computed tomography to assess rib cage mobility in humans. *(Chapter 7)*
18. Mueller G, Perret C, Michel F, Berger M, Hopman M.T.E. Rib cage mobility of individuals with chronic tetraplegia is reduced but not absent, whereas mobility of the diaphragm is intact. *(Chapter 8)*

Conference abstracts

1. Mueller G, Perret C. Isocapnic hyperpnoea training in wheelchair racing athletes. (2005) *Eur Resp J* 26 (Suppl 49): 108S (Poster, Annual Conference of the Europen Respiratory Society; September 17th - 21st 2005, Copenhagen, Denmark)
2. Mueller G, Perret C, Hofer P, Berger M, Michel F. Computed tomography to assess respiratory mechanics in tetraplegic patients. (2005) *Chest* 128 (Suppl.):388S (Poster, Chest Conference; October 29th - November 3rd 2005, Montréal, Canada)
3. Mueller G, De Groot S, Van der Woude L, Hopman MTE. Lung function during and after spinal cord injury rehabilitation. 11th Mini-Symposium 'Physical strain, work capacity and mechanisms of restoration of mobility in the rehabilitation of persons with SCI'; (Invited oral presentation; June 16th 2006, Groningen; The Netherlands)
4. Mueller G, Hofer P, Perret C, Michel F, Berger M and Hopman MTE. Differences in respiratory mechanics between tetraplegic and able bodied individuals. (2006) *J Spinal Cord Med*. 29:280 (Oral presentation, ASIA and ISCOS Joint Annual Conference; June 24th - 28th 2006, Boston, USA)
5. Mueller G, Perret C and Spengler CM. Optimal intensity for respiratory endurance training in patients with spinal cord injury. (2006) *J Spinal Cord Med*. 29: 262 (Oral presentation, ASIA and ISCOS Joint Annual Conference; June 24th - 28th 2006, Boston, USA)

6. Mueller G. Optimisation of exercise performance in wheelchair racing athletes. (2006) *Schw Z Sportmed Sporttraumat* 54(2):79 (Invited oral presentation, ECSS Annual Conference; July 5th - 8th 2006, Lausanne, Switzerland)
7. Mueller G, de Groot S, van der Woude L, Hopman M. Time-courses of Respiratory Function after SpinalCord Injury: A Prospective Cohort Study. ISCOS Conference Abstract Book (Oral presentation, ISCOS Annual Conference; June 27th - 30th 2007, Reykjavik, Iceland)
8. Mueller G, de Groot S, van der Woude L, Hopman M. Respiratory function in persons with a spinal cord injury one year after inpatient rehabilitation. ISCOS Conference Abstract Book (Poster, ISCOS Annual Conference; June 27th - 30th 2007, Reykjavik, Iceland)



Curriculum Vitae

Curriculum Vitae

Gabi Mueller was born on November 21st 1974 in Maennedorf, Switzerland. She grew up in Rapperswil and in 1994 she finished high school at the 'Gymnasium Wattwil'. Thereafter she was a professional kayaker for two years and won an olympic silver medal at the Olympic Games in Atlanta. From 1996 to 2000 she studied 'Sports' at the Swiss National Institute of Technology (ETH) in Zuerich and got her diploma in 2000. From 2000 to 2002 she completed two post graduate-courses in 'Training and Coaching' and 'Adapted Physical Activities'. From 1999 to 2003 she worked part time as national coach of the Swiss junior's kayak team. In 2001 she did a 10 month traineeship entitled 'clinical research in people with spinal cord injury' at the Swiss Paraplegic Centre Nottwil, Switzerland. From 2002 to 2003 she worked part-time for the department of sports medicine at the Swiss Paraplegic Centre Nottwil and got her 'Adapted Physical Activities' certificate in 2003. In August 2003 she applied for doing a PhD thesis at the department of physiology at the University of Nijmegen, supervised by Prof. dr. Maria T.E. Hopman. From September 2003 to May 2008 she worked as a PhD student at the Swiss Paraplegic Research Nottwil, Switzerland. During this time she was supervised by Maria Hopman by regular visits in Nijmegen and phone calls, but worked most time in Nottwil under supervision of Dr. Claudio Perret. Currently, she is still working at the Swiss Paraplegic Research in Nottwil, Switzerland.

"Life is a fragile, fleeting thing,
under any circumstances,
and living it can be comic or tragic,
weird or wonderful -
regardless of one's motor
limitations." (Maddox)